Screening, Monitoring, and Management of Interstitial Lung Disease Evidence Synthesis Report

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INTRODUCTION

Interstitial lung disease (ILD) constitutes a major source of morbidity and mortality among patients with systemic autoimmune rheumatic diseases (ARDs). Although all individuals with ARDs face the risk of developing ILD, those with systemic sclerosis (SSc), rheumatoid arthritis (RA), inflammatory myopathies, mixed connective tissue disease, and Sjogren's syndrome exhibit the highest risk. Also, ILD represents the second leading cause of death among adults with RA. Despite the substantial health burden of ILD and novel therapies, guidelines for diagnosing and managing ILD in patients with ARDs are currently lacking.

This systematic review was conducted to support the American College of Rheumatology in developing clinical practice guidelines for healthcare professionals who manage adult patients with ARDs who are at risk for or diagnosed with ILD. This review is structured around questions formulated by the Core Team responsible for the guidelines. These questions encompass five key areas: (i) screening for ILD in individuals with rheumatic diseases and at an increased risk of developing ILD; (ii) monitoring ILD progression and treatment complications; (iii) initiating ILD treatment; (iv) adjusting ILD treatment following disease progression under the first therapy; and (v) managing rapidly progressive ILD.

METHODS

Eligibility Criteria

Population of Interest

The population of interest included:

- Individuals aged ≥17 years
- Rheumatoid arthritis (RA), Systemic sclerosis (Scleroderma, SSc), Mixed Connective Tissue Disease (MCTD), Polymyositis, Dermatomyositis, MDA5 Dermatomyositis, Immune-Mediated Necrotizing Myositis, Antisynthetase syndrome, Sjogren's syndrome (screening questions)
- Diagnosed with ILD or progression of ILD (treatment and monitoring questions)

Exclusion criteria were:

- Individuals aged ≤16 years
- Juvenile scleroderma, juvenile systemic sclerosis, juvenile dermatomyositis, juvenile idiopathic arthritis, Sarcoidosis, Interstitial Pneumonia with Autoimmune Features (IPAF), ankylosing spondylitis, ANCA-associated vasculitis, Systemic lupus erythematosus, Undifferentiated connective tissue disease
- Idiopathic Pulmonary Fibrosis
- Idiopathic interstitial pneumonia
- Unclassifiable ILD
- Overlap syndromes (e.g., systemic scleroderma [SSc] + myositis, RA + SSc, etc.)

- Other populations, not mentioned in the "Included" section.

Critical outcomes

The critical outcomes, as prespecified by the Core Team, include the following:

- **Critical outcomes for screening questions:**
    - Diagnostic accuracy
    - Disease-related outcomes*
    - Diagnostic testing-related adverse events
- **Critical outcomes for monitoring questions:**
    - Responsiveness/sensitivity to change in the test
    - Disease-related outcomes*
    - Treatment-related serious adverse events†
    - Testing-related adverse events†
- **Critical outcomes for medical management questions**:
    - Disease-related outcomes*
    - Treatment-related adverse events†

*Disease-related outcomes included mortality, disability, and health-related quality of life. †Adverse events of interest included serious adverse events, toxicity leading to discontinuation, and other adverse reactions.
Surrogate outcomes were disease activity/disease progression defined by forced vital capacity (FVC), diffusion capacity for carbon monoxide (DLCO), CT thorax: the extent of disease, and disease progression.

Interventions

The following interventions were within the scope of this review:

- Pulmonary Function Tests (PFTs)
- History/physical alone (e.g., shortness of breath (dyspnea), functional class, and physician examination: crackles on auscultation)
- High-resolution CT Thorax
- 6-minute walk test distance
- Ambulatory desaturation
- Chest radiograph (chest x-ray)
- Bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy)
- Surgical lung biopsy
- csDMARDs: methotrexate, leflunomide, azathioprine, cyclophosphamide, mycophenolate, calcineurin inhibitors (tacrolimus, cyclosporine)

- bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), IL-6 receptor antagonists (tocilizumab, sarilumab), anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab), abatacept
- tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
- Others: Oral prednisone, intravenous methylprednisolone, intravenous immunoglobulin (IVIG), plasma exchange (plasmapheresis)
- Antifibrotics: Pirfenidone, Nintedanib
- Stem cell transplant (autologous, mesenchymal stem cells, hematopoietic, myeloablative, non-myeloablative)
- Lung Transplant

The following interventions were outside of the scope of this review:

- Vaccines: influenza; COVID-19; Measles, Mumps, and Rubella (MMR); pneumococcus vaccine
- Education (self-management of oxygen, ILD disease)
- Physiotherapy (chest physiotherapy, airway clearance, incentive spirometry), Exercise (aerobic, resistance training, yoga, tai chi), Pulmonary Rehabilitation (cardio-pulmonary rehabilitation, resistance training, in a center versus home)
- Oxygen (oxygen desaturation at rest, oxygen desaturation <88% with exercise)
- Palliative care (cough, pain, air hunger, end-stage, end-of-life planning, when to initiate, what to initiate)
- Smoking cessation
- Fundoplication
- Gastrointestinal Medications: proton pump inhibitors, H2 blockers, promotility agents
- Ibritumomab (is anti-CD20, but it is radioimmunotherapy)
- Basiliximab
- Other interventions not mentioned in the “Included” section above.

Study Design

For all questions related to monitoring and management, we used a best evidence approach in which randomized (RCTs) or non-randomized controlled trials were considered as first line evidence. In the absence of controlled trials, we considered evidence from other study designs (e.g., observational studies) that reported on the population and intervention of interest. To capture adverse events, we also considered open-label extension studies of RCTs or other longitudinal observational studies that focused on safety and tolerability. For questions that focus on assessing screening accuracy, we included studies without a control group, specifically cohort and cross-sectional studies. We also included existing systematic reviews and guidelines from other societies only to confirm that we have included all relevant references.

Information Sources, and Search Strategy

A search was conducted and updated on August 1, 2022, using the following databases: Ovid MEDLINE(R) and Epub Ahead Of Print, In-Process, In-Data Review & Other Non-Indexed Citations, Daily And Versions(R) (searched from 1946 to May 3, 2021); Ovid MEDLINE(R) ALL (Original Search: 1946 to 08/01/2022); Ovid Embase (Original Search: 1974 to 08/01/2022). All searchers were updated on January 6, 2023. We also supplemented database search with articles suggested by the Core Team members.

Study Selection

Two investigators independently assessed titles and abstracts of articles for potential inclusion. Subsequently, the full texts of these articles were obtained and independently evaluated by two investigators. To determine the final list of included or excluded articles, two more investigators reviewed the remaining full-text articles. In case of any disagreement, a consensus was reached through discussion.

Quality Assessment and Data Abstraction

We created a standardized table for data extraction in which one reviewer was responsible for extracting and evaluating data such as author, publication year, country, study type, patient characteristics, intervention type, and outcome data. For RCTs, data were obtained for control and intervention groups.

One researcher assessed individual study risk of bias (ROB). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool[1] was utilized to evaluate the ROB of diagnostic accuracy studies, while the Cochrane tool was employed to assess the ROB for RCTs (via GRADEPro)[2,3] and other study designs. A second review team member verified the accuracy of the extracted data and the ROB assessment to ensure consistency and reliability.

Certainty of Evidence Assessment

The certainty of the evidence was evaluated for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[4] which assigns one of four grades reflecting the level of confidence in the effect estimate: high, moderate, low, or very low. The initial quality assessment is based on the study design: RCTs start at high quality, while observational studies start at low quality. The quality of evidence was downgraded based on five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. We used the GRADE guidelines for rating the quality of evidence. The quality of the evidence was assessed by one review. A second reviewer from the literature review team verified the accuracy.

Of a particular note is the rating of evidence for surrogate outcomes. In alignment with GRADE recommendations, the Core Team characterized surrogate outcomes as those potentially linked to a clinically significant endpoint (e.g., mortality, functional improvement), but without necessarily correlating directly with it. For instance, forced vital capacity (FVC) and diffusing

capacity for carbon monoxide (DLCO) served as surrogate outcomes in this review. When assessing surrogate outcomes, we reduced the certainty of patient-important outcomes (such as symptoms and mortality) by one or two levels to account for indirectness.

Presentation of Effects

Treatment effects for binary outcomes were calculated and presented as both relative and absolute effects with a random effects model, when the meta-analysis was used. The effect for continuous outcomes was calculated using mean difference. All meta-analyses were conducted in RevMan.[5]

Relative effects convey the difference between the intervention and control groups in proportional terms. For instance, a 10% event rate in controls and a 5% event rate in the intervention equates to a 50% relative risk reduction ((10% - 5%) / 10%). Meanwhile, the same difference corresponds to a 5% absolute risk reduction (10% - 5% = 5%). Generally, absolute effects hold greater significance for patients.

In the tables, relative effects for dichotomous outcomes are expressed as either relative risk (RR) or odds ratio (OR). RR is the default effect size due to its ease of interpretation. However, in certain cases, RRs can result in implausible numbers when calculating absolute risk differences, prompting the use of ORs as an alternative to RRs.

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PICO 1: In people with rheumatic disease at increased risk of developing ILD, what is the impact of pulmonary function tests (PFTs) compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective case series, Manfredi et al., 2019,[1] suggests that the algorithm VECTOR (VELcro Crackles detecTOR) used to detect the presence of Velcro crackles in pulmonary sounds demonstrates good diagnostic accuracy for the presence of ILD among patients with rheumatoid arthritis.

Summary of Evidence:

We identified one study that provided indirect evidence reporting on the diagnostic accuracy of physical examination (Velcro crackles) and pulmonary function tests (PFTs) relative to high-resolution computed tomography (HRCT) among patients with rheumatoid arthritis (RA).[1] The methodological quality of the study was poor (high risk of bias) due to the potential for selection bias and lack of blinding of test readers. The certainty of the evidence was rated very low due to the serious risk of bias, indirectness, and imprecision.

Results from Observational Studies:

The study by Manfredi et al., 2019[1] reported on the diagnostic accuracy of pulmonary function tests and physical examination to detect ILD in a group of 137 patients with RA who had undergone HRCT for various reasons (more than half had HRCT performed due to symptoms of dyspnea or cough, abnormal lung findings/crackles, or abnormal X-Ray). Physical examination tests included 1) assessment for Velcro crackles on routine auscultation; and 2) VECTOR, a predefined computer algorithm for identifying Velcro crackles using an electronic stethoscope. In this study, diagnostic accuracy was highest by VECTOR (83.9%), followed by routine auscultation (67.2%), dyspnea (64.6%), dry cough (58.3%), and lowest with pulmonary function tests, DLCO<47% (54.9%), and FVC<70% (52.8%). VECTOR had the highest sensitivity (93.2%), followed by routine auscultation (69.1%) and dyspnea (41%). Sensitivity of DLCO> 47% (30.8%) and FVC<70% (20%) were low. Dry cough had the highest specificity (89.2%), followed by

FVC>70% (82.1%), dyspnea (81.3%), and DLCO<47% (80%). VECTOR and auscultation had lower specificity (76.9% and 65.7%). The diagnostic accuracy of VECTOR was not influenced by the duration of lung disease or by the extension of lung involvement.

Table 1-1. Evidence for PICO 1: Pulmonary function tests compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class, and physical examination: crackles on auscultation)

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Critical outcome: diagnostic accuracy						Very low[a]
Manfredi et al., 2019 The InsPIRAtE (INterStitial Pneumonia in Rheumatoid ArThritis with an Electronic device) study[1]	Retrospective case series	High Selection bias, measurement bias (test readers not blinded)	137 consecutive RA patients who had recently undergone HRCT Mean age at study entry: 67 years	Physical examinations: dyspnea, dry cough, VECTOR (VElcro Cackles detecTOR) Pulmonary function tests: DLCO<47%, FVC<70%	**Critical outcomes:** diagnostic accuracy **<u>Physical examination tests</u>** **Dyspnea**: diagnostic accuracy 64.6%, sensitivity 41.2%, specificity 81.3%. **Dry cough**: diagnostic accuracy 58.3%, sensitivity 15.1%, specificity 89.2%. **Velcro crackles by auscultation**: diagnostic accuracy 67.2%, sensitivity 69.1%, specificity 65.7%. **VECTOR**: diagnostic accuracy 83.9%. sensitivity 93.2%, specificity 76.9% **<u>Pulmonary function tests</u>** **DLCO<47%:** diagnostic accuracy 54.9%, sensitivity 30.8%, specificity 80%. **FVC<70%:** diagnostic accuracy 52.8%, sensitivity 20%, specificity 82.1%	

[a]Certainty of evidence downgraded for serious risk of bias, indirectness, and imprecision. The authors of the study indicate that the study population may not be representative of the general population of RA due to the higher rate of ILD observed in the study population.
DLCO: diffusion capacity of the lungs for CO; FVC: forced vital capacity

Table 1-2. PICO 1 Excluded Studies

Reference	Reason for Exclusion
Hoffman et al., 2022[2]	Not a comparator of interest
Pernot et al., 2012[3]	Not a comparator of interest
Salaffi et al., 2019[4]	Does not address PICO
Tashkin et al., 2017[5]	Does not address PICO
Roca et al., 2017[6]	Does not address PICO
Deheinzelin et al., 1996[7]	Not a comparator of interest
Fathi et al., 2004[8]	Not a comparator of interest
Bernstein et al., 2020[9]	Not a comparator of interest
Showalter et al., 2018[10]	Not a comparator of interest
Clements et al., 2004[11]	Not a comparator of interest

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PICO 2: In rheumatic disease patients at increased risk of developing ILD, what is the impact of high-resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective cohort study, Hax et al., 2017,[1] suggests that clinical algorithms primarily using lung auscultation and or chest X-Ray for the diagnosis of different extents of ILD on HRCT demonstrates relatively poor diagnostic performance at any extent of ILD on HRCT (sensitivity: 58.6%; specificity: 60.0%), but higher performance at 20% ILD on HRCT (sensitivity: 95.7%; specificity: 63.8%) among patients with systemic sclerosis.
    - Further findings indicate a positive association between the algorithm and mortality among patients with SSc who were positive for ILD (Hazard Ratio [HR] 2.71, 95% CI: 1.47 to 4.99).
- Evidence from one retrospective case series, Manfredi et al., 2019,[2] suggests that the algorithm VECTOR (VELcro Crackles detecTOR) used to detect the presence of Velcro crackles in pulmonary sounds demonstrates good diagnostic accuracy for the presence of ILD among patients with rheumatoid arthritis relative to HRCT.

Summary of Evidence:

We identified two studies poor quality studies (high risk of bias due to selection and measurement bias) that provided indirect evidence comparing the diagnostic accuracy of physical examination relative to high-resolution computed tomography (HRCT). The certainty of the evidence for the reported critical outcomes (diagnostic accuracy and mortality) were rated very low due to serious risk of bias, indirectness, and imprecision. The first study considered clinical algorithms to predict the presence and prognosis of systemic sclerosis (SSc)-interstitial lung disease (ILD) and to evaluate the association of the extent of ILD with mortality among SSc patients.[1] In this study three clinical algorithms, combining lung auscultation, chest X-ray, pulmonary function tests, and HRCT were applied relative to HRCT alone. For this PICO, we only considered the diagnostic accuracy of algorithm A (defined ILD if the study physician reported the presence of typical Velcro-like crackles on lung auscultation and/or chest X-Ray with findings suggestive of ILD or lung fibrosis) as it isolates the accuracy of physical examination relative HRCT. The results of HRCT scans were evaluated in the

following three ways: any extent of ILD, extent ≥10% of ILD, and extent ≥20% of ILD. Overall, a total of 177 consecutive patients with SSc met the inclusion criteria for this study and were evaluated.

The second study provided evidence reporting on the diagnostic accuracy of physical examination (Velcro crackles) relative to HRCT among patients with rheumatoid arthritis (RA).[2] The study by Manfredi et al. reported on the diagnostic accuracy of physical examination to detect ILD in a group of 137 patients with RA who had undergone HRCT for various reasons (more than half had HRCT performed due to symptoms of dyspnea or cough, abnormal lung findings/crackles, or abnormal X-Ray).[2] Physical examination tests included 1) assessment for Velcro crackles on routine auscultation; and 2) VECTOR, a predefined computer algorithm for identifying Velcro crackles using an electronic stethoscope.

Results from Observational Studies:

The findings of the first study by Hax et al., 2017[1] indicated that 37.3% of patients with SSc were positive for ILD based on the physical examination compared to 57.1% on HRCT. The findings of the algorithm suggest that physical examination was most accurate in diagnosing ILD when HRCT extent of ILD was ≥20% (sensitivity: 95.7, 95% CI: 78.3 to 99.8, specificity: 63.8, 95% CI: 58.0–65.1; positive likelihood ratio: 2.64, 95% CI: 1.86–2.86, negative likelihood ratio: 0.07, 95% CI: 0.01–0.37, accuracy: 71.7). It was least accurate in the presence of any extent of ILD on HCRT (sensitivity: 58.6, 95% CI: 49.9–66.6; specificity: 60.0; 95% CI: 45.5–73.3; +likelihood ratio: 1.47, 95% CI: 0.92–2.49; -likelihood ratio: 0.69, 95% CI: 0.45–1.10; accuracy: 59.1). Further findings indicate a positive association between the algorithm and mortality among patients with SSc who were positive for ILD (HR: 2.71, 95% CI: 1.47 to 4.99).

In the other study by Manfredi et al., 2019[2] that measured diagnostic accuracy, sensitivity, and specificity of physical examination tests (dyspnea, dry cough, VECTOR (VElcro Crackles detecTOR) with HRCT as a reference test, the overall diagnostic accuracy was highest by VECTOR (83.9%), following by dyspnea (58.3%), and dry cough (58.3%). The dry cough had the highest sensitivity (89.2%), followed by dyspnea (81.3%); VECTOR and Velcro had the lowest sensitivity (76.9% and 65.7%). The highest specificity was in VECTOR (93.2%) and Velcro crackles (69.1%), lower in dyspnea (41.2%), and the lowest in dry cough test (15.1%).

Table 2-1. Evidence for PICO 2: High-resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation)

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Critical outcome: Diagnostic accuracy						Very low[a]
Hax et al., 2017[1]	Retrospective cohort study	High Selection bias, unclear if index test readers were blinded, unclear if all patients underwent all index testing (e.g., chest X-ray)	177 patients with systemic sclerosis (SSc) Age (ILD patients): 51.8 (13.6) % Females: 82%	Three algorithms with algorithm A relevant to PICO 2: A: defined ILD if the study physician reported the presence of typical velcro-like crackles on lung auscultation and/or chest X-ray with findings suggestive of ILD or lung fibrosis **Reference**: high resolution computed tomography (HRCT)	Positive for ILD on physical examination 66/107 (37.3%) Positive for ILD on HRCT 101/177 (57.1%) Findings reported as sensitivity (SE); specificity (SP), positive likelihood ratio (+LR); negative likelihood ratio (-LR), accuracy **In relation to presence of any extent of ILD on HRCT** (n=93) **Algorithm A:** SE: 58.6, 95% CI: 49.9–66.6; SP: 60.0; 95% CI: 45.5–73.3; +LR: 1.47, 95% CI: 0.92–2.49; -LR: 0.69, 95% CI: 0.45–1.10; accuracy: 59.1 **In relation to the extent ≥10% of ILD on HRCT** (n= 92) **Algorithm A:** SE: 89.3, 95% CI: 73.4–97.1; SP: 65.6, 95% CI: 58.7–69.0, +LR: 2.60, 95% CI: 1.78–3.14; -LR: 0.16, 95% CI: 0.04–0.45, accuracy: 72.8 **In relation to the extent ≥20% of ILD on HRCT** (n= 92) **Algorithm A:** SE: 95.7, 95% CI: 78.3–99.8, SP: 63.8, 95% CI: 58.0–65.1; +LR: 2.64, 95%	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					CI: 1.86–2.86, -LR: 0.07, 95% CI: 0.01–0.37, accuracy: 71.7 **In relation to extensive disease as proposed by Goh et al.—using for indeterminate cases an extent of 10–30% on HRCT** (n =92) **Algorithm A:** SE: 94.7, 95% CI: 74.1–99.7, SP: 58.9, 95% CI: 53.5–60.2, +LR: 2.30, 95% CI: 1.60–2.51, -LR: 0.09, 95% CI: 0.01–0.48, accuracy: 66.3	
Manfredi et al., 2019 The InsPIRAtE (INterStitial Pneumonia in Rheumatoid ArThritis with an Electronic device) study [2]	Retrospective case series	High High selection bias, measurement bias (test readers not blinded)	137 consecutive RA patients who had recently undergone HRCT Mean age at study entry: 67 years	Physical examinations: dyspnea, dry cough, VECTOR (VElcro Cackles detecTOR) Pulmonary function tests: DLCO<47%, FVC<70%	**Critical outcomes:** diagnostic accuracy **<u>Physical examination tests</u>** **Dyspnoea**: diagnostic accuracy 64.6%, sensitivity 41.2%, specificity 81.3%. **Dry cough**: diagnostic accuracy 58.3%, sensitivity 15.1%, specificity 89.2%. **Velcro crackles by auscultation**: diagnostic accuracy 67.2%, sensitivity 69.1%, specificity 65.7%. **VECTOR**: diagnostic accuracy 83.9%. sensitivity 93.2%, specificity 76.9%	
Critical outcome: Mortality						Very low[a]
Hax et al., 2017[1]	Retrospective cohort study	High Selection bias, unclear if	177 patients with systemic sclerosis (SSc)	Three algorithms with algorithm A relevant to PICO 2: A: defined ILD if the study physician reported the	**Association with mortality** Algorithm A: Hazard ratio: 2.71, 95% CI: 1.47 to 4.99, shows a positive association	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
		index test readers were blinded, unclear if all patients underwent all index testing (e.g., chest X-ray)	Age (ILD patients): 51.8 (13.6) % Females: 82%	presence of typical velcro-like crackles on lung auscultation and/or chest X-ray with findings suggestive of ILD or lung fibrosis **Reference**: high resolution computed tomography (HRCT)	with mortality in patients with ILD.	

[a]Certainty of evidence downgraded for risk of bias, indirectness, and imprecision

Table 2-2. PICO 2: Excluded Studies

Reference	Reason for Exclusion
Hoffman et al., 2022[3]	Not a comparator of interest
Biederer et al., 2004[4]	No outcomes of interest
Aubart et al., 2011[5]	No intervention of interest
Launay et al., 2006[6]	No outcomes of interest
Lewszuk et al., 2008[7]	Not a comparator of interest
Salaffi et al., 2019[8]	Not a comparator of interest
Lucchino et al., 2020[9]	Not a comparator of interest
Tashkin et al., 2017[10]	No outcomes of interest
Fathi et al., 2008[11]	Not a comparator of interest
Roca et al., 2017[12]	No outcomes of interest
Fathi et al., 2004[13]	No outcomes of interest
Guisado-Vasco et al., 2019[14]	Wrong study design
Clements et al., 2004[15]	Not a comparator of interest

Reference	Reason for Exclusion
Frauenfelder et al., 2014[16]	Not a comparator of interest

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PICO 3: In rheumatic disease patients at increased risk of developing ILD, what is the impact of 6-minute walk test distance compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 4: In rheumatic disease patients at increased risk of developing ILD, what is the impact chest radiograph compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 4-1. PICO 4: Excluded Studies

Reference	Reason for exclusion
Hoffman et al., 2022[1]	Does not address PICO
Goggings et al., 2019[5]	No outcomes of interest
Hax et al., 2017 [2]	Does not address PICO
Pernot et al., 2012[7]	No outcomes of interest
Fathi et al., 2008[9]	No outcomes of interest
Lewszuk et al., 2008, [6]	No outcomes of interest
Fathi et al., 2004[8]	No outcomes of interest
Dawson et al., 2001[4]	Does not address PICO
Witt et al., 1996[3]	No outcomes of interest

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PICO 5: In rheumatic disease patients at increased risk of developing ILD, what is the impact of ambulatory desaturation compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 6: In rheumatic disease patients at increased risk of developing ILD, what is the impact of chest radiograph compared to high resolution CT thorax on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- Evidence from one case-control study[1] suggests that chest X-ray alone demonstrates a low sensitivity (64.0%) and moderate specificity (73.6%) relative to HRCT for identifying ILD among patients with inflammatory rheumatic diseases.
- Evidence from one retrospective cohort study[2] suggests that clinical algorithms primarily using lung auscultation and or chest X-ray for the diagnosis of different extents of ILD on HRCT demonstrates relatively poor diagnostic performance at any extent of ILD on HRCT (sensitivity: 58.6%; specificity: 60.0%), but higher performance at 20% ILD on HRCT (sensitivity: 95.7%; specificity: 63.8%) among patients with systemic sclerosis.
    - Further findings indicate a positive association between the algorithm and mortality among patients with SSc who were positive for ILD (hazard ratio: 2.71, 95% CI: 1.47 to 4.99).
- Evidence from a small case series study[3] reports a sensitivity of 80% and specificity of 100% on chest X-ray for diagnosis of ILD in patients with systemic sclerosis.

Summary of Evidence:

We identified three studies poor quality (high risk of bias, see Table 6-1) studies that provided evidence for PICO 6. The case-control study evaluated a stepwise algorithm to diagnose ILD among 126 patients with inflammatory rheumatic diseases (IRD) (Hoffman et al., 2022[1]). All patients underwent pulmonary function testing and chest radiography. HRCT was subsequently performed in patients showing at least one pathological finding. For this PICO, we focused on the diagnostic findings of chest radiography relative to HRCT. The second study considered clinical algorithms to predict the presence and prognosis of systemic sclerosis (SSc)-interstitial lung disease (ILD) and to evaluate the association of the extent of ILD with mortality in SSc patients (Hax et al., 2017[2]). In this study, three clinical algorithms, combining lung auscultation, chest tests, pulmonary function tests, and HRCT, were applied relative to HRCT alone. For this PICO, we only considered the diagnostic accuracy of algorithm A (defined ILD if the study physician reported the presence of typical Velcro-like crackles on lung auscultation and/or chest X-ray with findings suggestive of ILD or lung fibrosis)

as it isolates the accuracy of chest X-ray relative HRCT. The results of CT scans were evaluated in the following three ways: any extent of ILD, extent ≥10% of ILD, and extent ≥20% of ILD. Overall, a total of 177 consecutive patients with SSc met the inclusion criteria for this study and were evaluated. The final study was a smaller case series (n=42) study that reported on the diagnostic accuracy of chest X-ray and biological serum markers relative to HRCT (Takahashi et al., 2000[3]). We only report on the findings for chest X-ray relative to HRCT.

Summary of Findings:

The findings of the first study by Hoffman et al., 2022[1] showed a sensitivity of 64.2% and specificity of 73.4% for chest X-ray relative to HRCT (sensitivity of 100%; specificity of 55.3%) in detecting ILD among patients with IRD. These findings were similar when considering IRD disease type (i.e., connective tissue disease, vasculitis, and myositis). The findings of the study by Hax et al., 2017[2] indicated that 37.3% of patients with SSc were positive for ILD based on physical examination compared to 57.1% on HRCT. The findings of the algorithm suggest that physical examination with chest X-ray was most accurate in diagnosing ILD when HRCT extent of ILD was ≥20% (sensitivity: 95.7, 95% CI: 78.3–99.8, specificity: 63.8, 95% CI: 58.0–65.1; positive likelihood ratio: 2.64, 95% CI: 1.86–2.86, negative likelihood ratio: 0.07, 95% CI: 0.01–0.37, accuracy: 71.7). It was least accurate in the presence of any extent of ILD on HCRT (sensitivity: 58.6, 95% CI: 49.9–66.6; specificity: 60.0; 95% CI: 45.5–73.3; +likelihood ratio: 1.47, 95% CI: 0.92–2.49; -likelihood ratio: 0.69, 95% CI: 0.45–1.10; accuracy: 59.1). Further findings indicate a positive association between the algorithm and mortality among patients with SSc who were positive for ILD (Hazard ratio: 2.71, 95% CI: 1.47 to 4.99). Finally, the findings of the smaller study by Takahashi et al., 2000[3] reports a sensitivity of 80% and specificity of 100% on chest X-ray for diagnosis of ILD in patients with systemic sclerosis. However, patients in this study had more advanced disease compared to the other studies.

Table 6-1. Evidence for PICO 6: Impact of chest radiograph compared to high resolution CT thorax

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Critical outcome: Diagnostic accuracy						Very low[a]
Hoffman et al., 2022[1]	Case-control study	High Unclear blinding of test readers, small sample of patients with ILD, not all patients received reference test-HRCT	126 patients with newly diagnosed inflammatory rheumatic disease (IRD) N=63 (50%) with ILD N=63 (50%) without ILD **Characteristics of ILD patients** Age: Median: 58.6 years % Female: 63% Inflammatory rheumatic diseases with ILD: i. Connective tissue disease: 35 (55.6%) i. Small vessel vasculitis 16 (25.4%) i. Myositis 12 (19.0%)	Chest radiograph alone compared to high-resolution computed tomography	**Chest X ray** Sensitivity: 64.2% Specificity: 73.6% +Likelihood ratio: 2.43 -Likelihood ratio: 0.49 **Subgroups** Connective tissue disease: sensitivity: 63.3%, specificity: 73.6% Small vessel vasculitis: sensitivity: 61.5%, specificity: 73.6% Myositis: sensitivity: 70.0%; specificity: 73.6% **HRCT** Sensitivity: 100% Specificity: 55.3% +Likelihood ratio: 2.24 -Likelihood ratio: <0.01	
Hax et al., 2017[2]	Retrospective cohort study	High Selection bias, unclear if index test readers were blinded, unclear if all patients	177 patients with systemic sclerosis (SSc) Age (ILD patients): 51.8 (13.6) % Females: 82%	Three algorithms with algorithm A relevant to PICO 6: A: defined ILD if the study physician reported the presence of typical velcro-like crackles on lung auscultation and/or chest X-ray with findings suggestive of ILD or lung fibrosis	Positive for ILD on physical examination 66/107 (37.3%) Positive for ILD on HRCT 101/177 (57.1%) Findings reported as sensitivity (SE); specificity (SP), positive likelihood ratio (+LR); negative likelihood ratio (-LR), accuracy	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
		underwent all index testing (e.g., chest X-ray)		**Reference**: high resolution computed tomography (HRCT)	**In relation to presence of any extent of ILD on HRCT** (n=93) **Algorithm A:** SE: 58.6, 95% CI: 49.9–66.6; SP: 60.0; 95% CI: 45.5–73.3; +LR: 1.47, 95% CI: 0.92–2.49; -LR: 0.69, 95% CI: 0.45–1.10; accuracy: 59.1 **In relation to the extent ≥10% of ILD on HRCT** (n= 92) **Algorithm A:** SE: 89.3, 95% CI: 73.4–97.1; SP: 65.6, 95% CI: 58.7–69.0, +LR: 2.60, 95% CI: 1.78–3.14; -LR: 0.16, 95% CI: 0.04–0.45, accuracy: 72.8 **In relation to the extent ≥20% of ILD on HRCT** (n= 92) **Algorithm A:** SE: 95.7, 95% CI: 78.3–99.8, SP: 63.8, 95% CI: 58.0–65.1; +LR: 2.64, 95% CI: 1.86–2.86, -LR: 0.07, 95% CI: 0.01–0.37, accuracy: 71.7 **In relation to extensive disease as proposed by Goh et al.—using for indeterminate cases an extent of 10–30% on HRCT** (n =92) **Algorithm A:** SE: 94.7, 95% CI: 74.1–99.7, SP: 58.9, 95% CI: 53.5–60.2, +LR: 2.30, 95% CI: 1.60–2.51, -LR: 0.09, 95% CI: 0.01–0.48, accuracy: 66.3	
Takahashi et al., 2000[3]	Prospective observational study	High Selection bias (small	42 patients with progressive systemic sclerosis	Index test: Chest radiograph	<u>Chest X ray</u> Sensitivity: 80% (24/30) Specificity: 100% (12/12) 100%	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
		sample of patients with more severe disease)	Average age is 54.9 (±9.3) 90.5% female	Reference test: High-resolution computed tomography		
Critical outcome: Mortality						Very low[a]
Hax et al., 2017[2]	Retrospective cohort study	High Selection bias, unclear if index test readers were blinded, unclear if all patients underwent all index testing (e.g., chest X-ray)	177 patients with systemic sclerosis (SSc) Age (ILD patients): 51.8 (13.6) % Females: 82%	Three algorithms with algorithm A relevant to PICO 6: A: defined ILD if the study physician reported the presence of typical velcro-like crackles on lung auscultation and/or chest X-ray with findings suggestive of ILD or lung fibrosis **Reference**: high resolution computed tomography (HRCT)	**Association with mortality** Algorithm A: Hazard ratio: 2.71, 95% CI: 1.47 to 4.99, shows a positive association with mortality in patients with ILD.	

[a]Certainty of the evidence for critical outcomes downgraded due to high risk of bias (largely due to selection and measurement bias), indirectness, and imprecision

HRCT: High resolution computerized tomography, ILD: interstitial lung disease, CTD: Connective tissue disease.

Table 6-2. PICO 6 Excluded Studies

Reference	Reason for Exclusion
Robles-Perez et al., 2020[14]	No intervention of interest
Bernstein et al., 2020[12]	No intervention of interest
Guisado-Vasco et al., 2019[16]	No intervention of interest

Reference	Reason for Exclusion
Showalter et al., 2018[13]	No intervention of interest
Kim et al., 2017[7]	No outcomes of interest
Suliman et al., 2015[15]	No intervention of interest
Burge et al., 2017[11]	No intervention of interest
Pernot et al., 2012[8]	Small sample size
Ayhan et al., 2006[10]	Small sample size
Fathi et al., 2004[9]	Small sample size
Clements et al., 2004[17]	No intervention of interest
Komocsi et al., 2001[4]	No outcomes of interest
Witt et al., 1996[5]	No outcomes of interest
Nishimura et al., 1993[6]	Population not of interest

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PICO 7: In rheumatic disease patients at increased risk of developing ILD, what is the impact of pulmonary function tests (PFTs) compared to ambulatory desaturation on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 7-1. PICO 7 Excluded Studies

Reference	Reason for Exclusion
Hoffman et al., 2022[1]	No outcomes of interest
Bernstein et al., 2020[3]	No outcomes of interest
Showalter et al., 2018[4]	No outcomes of interest
Pernot et al., 2012[2]	No outcomes of interest
Clements et al., 2004[5]	No outcomes of interest

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PICO 8: In rheumatic disease patients at increased risk of developing ILD, what is the impact of high-resolution CT thorax compared to PFTs on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key findings:

- Evidence from five studies suggests that pulmonary function tests used alone may be insufficient to detect ILD among patients with newly diagnosed rheumatic diseases, including connective tissue disease (systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, Sharp syndrome), vasculitis, myositis, systemic sclerosis, and rheumatoid arthritis (Hoffman et al., 2022;[1] Bernstein et al., 2020;[2] Manfredi et al., 2019;[3] Showater et al., 2015;[4] Suliman et al., 2015[4]).
    - According to Bernstein et al., 2019, the combination of FVC < 80% predicted or DLCO < 80% predicted performed better than any individual parameter, with a sensitivity of 85% for detecting ILD on HRCT in patients with systemic sclerosis.

Summary of Evidence:

Our searches identified five studies that reported findings of the accuracy of pulmonary function tests relative to high-resolution computed tomography. The most recent case-control study by Hoffman et al included ILD among 126 patients with newly diagnosed inflammatory rheumatic diseases (IRD).[1] This study reports on the accuracy of PFTs, chest X-ray, and HRCT alone and in different combinations (PFT plus chest X-ray, PFT plus HRCT, and PFT plus chest X-ray followed by HRCT). All patients underwent pulmonary function testing and chest radiography. For this PICO, we focused on the diagnostic findings of PFTs relative to HRCT. Three studies reported the performance characteristics of PFTs for detecting ILD in patients with newly diagnosed systemic sclerosis (SSc) (Bernstein et al., 2020,[2] Showater et al., 2015,[5] Suliman et al., 2015[4]). The final study reported on the diagnostic accuracy of DLCO at <47% and FVC at <70% to detect ILD in 137 patients with rheumatoid arthritis (RA) (Manfredi et al., 2019[3]).

Summary of Findings:

Findings of the most recent study by Hoffman, T. et al., 2022,[1] indicated that DLCO < 80% revealed a sensitivity of 83.6% and a specificity of 45.8% for detecting ILD in patients with IRD.[1] These findings are in accordance with data reported by Bernstein et al., 2019[2] yielding a sensitivity of 80.0% and specificity of 51.0% in detecting ILD in early SSc. In addition, other studies of patient with

SSc showed similar sensitivities and specificities for other PFT parameters: Showalter et al., 2015[6] and Suliman et al., 2015[4] demonstrated a sensitivity and a specificity of 37.5 to 69.0% and 73.0 to 92.0%, respectively, for FVC < 80%. According to Bernstein et al., 2020[2] DLCO < 80% predicted had better sensitivity than FVC < 80% predicted or TLC < 80% predicted for the detection of ILD on HRCT in patients with early dcSSc. The combination of FVC < 80% predicted or DLCO < 80% predicted performed better than any individual parameter, with a sensitivity of 85% for the detection of ILD on HRCT in this population.

Table 8-1. Evidence for PICO 8: High-resolution CT thorax compared to PFTs on diagnostic accuracy

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Critical outcome: diagnostic accuracy						Low[1]
Hoffman et al., 2022[1] PICO 8	Case-control study	High ROB Unclear selection bias (uses elements of case control design); High blinding (blinding of test readers not reported); high verification (not all pts received HRCT)	63 IRD patients with ILD ILD patients Age: 53.8 % Female: 63% IRD: Connective tissue disease (systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, and Sharp syndrome): 55.6% Vasculitis:24.4% Myositis: 19.0%	High resolution CT (HRCT) compared to pulmonary function tests (PFTs) PFTs include Diffusing capacity for carbon monoxide (DLCO), Forced expiratory volume in 1 s (FEV1), Forced vital capacity (FVC), Total lung capacity (TLC), Transfer factor of the lung for carbon monoxide (TLCO)	Diagnostic procedure parameter: AUC (95% CI) Cut-off for Sensitivity (SE), Specificity (SP), Positive likelihood ratio (LR+), Negative likelihood ratio (LR−) **PFT Alone** DLCO: AUC: 0.772 (0.690–0.855) ● Cut-off: < 80%: SE: 83.6%; SP: 45.8%, LR+: 1.54; LR- 0.36 ● Cut-off: < 70%: SE: 67.2%; SP: 76.3%: LR+: 2.84; LR-: 0.43 TLC: AUC: 0.707 (0.610–0.803) ● < 80%: SE: 32.1%, SP: 94.6%, LR+ 5.94, LR- 0.72 ● < 70%: SE: 23.2%, SP: 100.0%, LR+: > 100, LR-:0.77 TLCO: AUC: 0.686 (0.591–0.781) ● < 80%: SE: 57.6%, SP: 67.8%, LR+: 1.79, LR-: 0.63 ● < 70%: SE: 32.2%, SP: 84.7%, LR+: 2.10, LR-: 0.80 FVC: AUC: 0.648 (0.548–0.747)	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					• < 80%: SE: 47.5%, SP: 78.7%, LR+ 2.23, LR- 0.67 • < 70%: SE: 32.2%, SP: 91.8%, LR+: 3.93, LR- 0.74 FEV1: AUC: 0.629 (0.526–0.732) • < 80%: SE: 49.2%, SP: 82.0%, LR+ 2.73, LR- 0.62 • < 70%: SE: 33.9%, SP: 91.1%, LR+ 3.81, LR- 0.73 **HRCT** • SE: 100%, SP: 55.3%, LR+ 2.24; LR- <001	
Bernstein et al., 2020[2] Prospective Registry of Early Systemic Sclerosis (PRESS)	Retrospective cohort study	High ROB Unclear spectrum bias, high blinding, high verification (not all patients received HRCT)	212 patients with early systemic sclerosis (SSc) screened for the detection of ILD. All participants enrolled in PRESS between April 2012 and January 2019 who underwent spirometry and HRCT were included. Age: 51.7 % Female: 67.9%	Pulmonary function tests: FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide HRCT as a reference test	54% of patients had radiographic evidence of ILD. FVC < 80%: N=212; Sensitivity 63%; Specificity 68%; PPV 70%; NPV 61%; +LR 2.0; -LR 0.5; FPR 0.32; FNR 0.37. TLC < 80%: N=146; Sensitivity 46%; Specificity 77%; PPV 74%; NPV 51%; +LR 2.0; -LR 0.7; FPR 0.23; FNR 0.54. DLCO < 80%: N=200; Sensitivity 80%; Specificity 51%; PPV 66%; NPV 68%; +LR 1.6; -LR 0.4; FPR 0.49; FNR 0.20. Combined FVC or DLCO < 80%: N=199; Sensitivity 85%; Specificity 42%; PPV 64%; NPV 70%; +LR 1.5; -LR 0.4; FPR 0.58; FNR 0.15. Combined FVC or TLC or DLCO < 80%: N=143; Sensitivity 85%; Specificity 42%; PPV 68%; NPV 66%; +LR 1.5; -LR 0.4; FPR 0.58; FNR 0.15.	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Manfredi et al., 2019[3]	Retrospective case series The InsPIRAtE (INterStitial Pneumonia in Rheumatoid ArThritis with an Electronic device) study	Unclear ROB High spectrum bias	137 consecutive patients with rheumatoid arthritis (RA) who had recently undergone HRCT Age: 67.9% Male/female ratio: 1/183	PFTs: DLCO<47%, FVC<70% HRCT as a reference test	43% of patients identified with ILD DLCO<47%: diagnostic accuracy 54.9%, sensitivity 30.8%, specificity 80%. FVC<70%: diagnostic accuracy 52.8%, sensitivity 20%, specificity 82%%	
Showalter et al., 2018[5]	Case series	Unclear ROB Unclear spectrum bias; unclear blinding	265 patients with systemic sclerosis (SSc) Age: 50 % Female: 82%	Pulmonary function tests: FVC, DLCO, combined FVC and DLCO HRCT as a reference test	71% of patients identified as having radiographic ILD **FVC % predicted**, n = 265, ● < 80 (conventional and optimal): Sensitivity 69%; Specificity 73%; PPV 86%; NPV 49%. **DLCO % predicted**, n = 214: ● < 60 (conventional): Sensitivity 58%; Specificity 70%; PPV 82%; NPV 41%. ● < 62 (optimal): Sensitivity 60%; Specificity 70%; PPV 83%; NPV 42%. ● < 70 (alternative): Sensitivity 80%; Specificity 51%; PPV 80%; NPV 52%. ● < 80 (alternative): Sensitivity 92%; Specificity 32%; PPV 77%; NPV 63%. **Combination of PFT thresholds % predicted**, n = 214 ● FVC < 80 and DLCO < 60: Sensitivity 46%; Specificity 81%; PPV 85%; NPV 38%.	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					• FVC < 80 or DLCO < 60: Sensitivity 79%; Specificity 57%; PPV 82%; NPV 53%. • FVC < 80 and DLCO < 62: Sensitivity 49%; Specificity 81%; PPV 86%; NPV 40%. • FVC < 80 or DLCO < 62: Sensitivity 80%; Specificity 56%; PPV 81%; NPV 53%. • FVC < 80 and DLCO < 65: Sensitivity 53%; Specificity 78%; PPV 85%; NPV 41%. • FVC < 80 or DLCO < 65: Sensitivity 82%; Specificity 46%; PPV 78%; NPV 52%. • FVC < 80 and DLCO < 70: Sensitivity 61%; Specificity 76%; PPV 86%; NPV 45%. • FVC < 80 or DLCO < 70: Sensitivity 87%; Specificity 43%; PPV 78%; NPV 0.57. • FVC < 80 and DLCO < 80: Sensitivity 66%; Specificity 73%; PPV 85%; NPV 47%. • FVC < 80 or DLCO < 80: Sensitivity 94%; Specificity 27%; PPV 76%; NPV 65%.	
Suliman et al., 2015[4]	Case series	Unclear ROB	102 patients with systemic sclerosis (SSc) Age: 58.5	PFT HRCT as a reference test	64 (63.0%) showed significant ILD on HRCT, while only 27 (26.0%) had an FVC. 40 (53.0%) of 75 patients with normal FVC values showed significant ILD on HRCT. Thus, when FVC alone was used for screening and early detection	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
		Unclear spectrum bias	% Female: 77.0%		of ILD, there was a high false-negative rate of 62.5%. ● **FVC<80%:** False-negative rate 62.5% (40/64); False-positive rate 7.9% (3/38); Sensitivity 37.5% (0.3–0.5); Specificity 92% (0.8–1.0); Positive LR 4.7 (1.5–4.7); Negative LR 0.7 (0.5–0.8). ● **FVC<80% or DFVC>10%:** False-negative rate 44.7% (21/47); False-positive rate 31.0% (6/19); Sensitivity 55.3% (0.4–0.7); Specificity 68.4% (0.5–0.8); Positive LR 1.7 (0.8–3.5); Negative LR 0.7 (0.4–1.0). ● **FVC<80% or TLC<80%:** False-negative rate 55.0% (35/64); False-positive rate 13.2% (5/38); Sensitivity 45.0% (0.3–0.5); Specificity 86.0% (0.7–0.9); Positive 3.4 (1.4–8.1); Negative LR 0.6 (0.4–0.8). ● **FVC<80%or DLCO<70%:** False-negative rate 41.0% (26/64); False-positive rate 34.3% (13/38); Sensitivity 59.0% (0.4–0.7); Specificity 65.8% (0.5–0.7); Positive LR 1.7 (1.0–2.8); Negative LR 0.6 (0.4–0.9). ● **FVC< 80% or TLC<80% or DLCO<70%:** False-negative rate 37.0% (24/64); False-positive rate 37.0% (14/38); Sensitivity 62.0% (0.5–0.7); Specificity 63.0% (0.4–0.7);	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					Positive LR 1.7 (1.0–2.6); Negative LR 0.6 (0.4–0.8). • **FVC<80% or DFVC>10% or TLC<80% or DLCO<70% and FEV1/FVC.0.7**: False-negative rate 27.0% (15/54); False-positive rate 56.0% (13/23); Sensitivity 72.0% (0.6–0.8); Specificity 43.0% (0.3–0.6); Positive LR 1.3 (0.9–1.9); Negative LR 0.6 (0.3–1.2)	
Additional Studies (not used to support GRADE rating, but that may provide additional information)						
Salaffi et al., 2019[7]	Retrospective case series	High	151 patients with rheumatoid arthritis (RA): 122 without ILD; 29 with ILD Age: 54 years	DLCO FVC HRCT as a reference test	ILD detected in 29 patients out of 151 (19.2%) DLCO (% predicted): AUC 0.811± SE 0.0377, 95% CI 0.737–0.885 FVC (% predicted): AUC 0.777± SE 0.0426, 95% CI 0.684–0.851	NA
Pernot et al., 2012[8]	Case-control study	High	35 patients with systemic sclerosis (SSc) compared to 16 healthy controls Age: 66 years Female/male ratio: 11/2 of patients with SSc	To determine whether diffusion capacity of the lungs for carbon monoxide (DLCO) partitioned into membrane conductance for CO (DmCO) and alveolar capillary blood volume (Vcap) could provide more sensitive clues to ILD than current PFTs Pulmonary function tests: DmCO/Vcap;	ROC analysis showed that a cutoff value of 0.27 for the DmCO:Vcap ratio identified SSc-ILD+ patients with a sensitivity of 85% and a specificity of 100% (p<0.0001). The sensitivity of DLCO, with a cutoff of 67% of the predicted value, was 54%, and the overall specificity was 91% (AUC = 0.75, p = 0.005). Comparison of ROC analysis showed that the DmCO/ Vcap ratio was more sensitive and specific for identifying SSc-ILD+ than TLC, vital capacity and DLCO (p<0.01).	NA

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
				DLCO HRCT as a reference test		

[1]Certainty of evidence downgraded for serious risk of bias (primarily due to selection and measurement bias in some studies) and indirectness.

Table 8-2. PICO 8 Excluded Studies

Reference	Reason for Exclusion
Abdelwahab et al., 2022[27]	Does not address PICO
Murdaca et al., 2021[19]	Does not address PICO
Carvalho et al., 2020[23]	Does not address PICO
Robles-Perez et al., 2020[20]	Does not address PICO
Guisado-Vasco et al., 2019[21]	Does not address PICO
Frauenfelder et al., 2014[24]	Does not address PICO
Moghadam et al., 2011[9]	Does not address PICO
Rosas et al., 2011[10]	Does not address PICO
Morganroth et al., 2010[15]	Does not address PICO
Fathi et al., 2008[25]	Does not address PICO
Kostopoulos et al., 2008[18]	Does not address PICO
Camiciottoli et al., 2007[17]	Does not address PICO
Launay et al., 2006[13]	Does not address PICO
Lee et al., 2005[14]	Does not address PICO
Bodolay et al., 2005[11]	Does not address PICO
Clements et al., 2004[22]	Does not address PICO
Fathi et al., 2004[16]	Does not address PICO
Dawson et al., 2001[12]	Does not address PICO
McDonagh et al., 1994[26]	Does not address PICO

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PICO 9: In rheumatic disease patients at increased risk of developing ILD, what is the impact of high-resolution CT thorax and PFTs compared to PFTs alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- Evidence from one case-control study (Hoffman et al., 2022[1]) indicates that reduced DLCO<80% and/or abnormal chest x-ray following by HRCT yielded the highest sensitivity and specificity in detecting ILD among patients with newly diagnosed IRD (Sensitivity: 89.5%, specificity: 65.8%). These findings suggest that the diagnostic accuracy of DLCO <80% plus HRCT is higher than DLCO <80% (or any other PFT) used alone.

Summary of Evidence:

We identified one case-control study (Hoffman et al., 2022[1]) that reported on the diagnostic accuracy of pulmonary functions tests alone and in combination with high-resolution computed tomography. Hoffman et al., (2022) evaluated a stepwise algorithm to diagnose ILD among 126 patients with newly diagnosed inflammatory rheumatic diseases (IRD). This study reports on the accuracy of pulmonary function tests (PFTs), chest X-ray, and HRCT alone and in different combinations (PFT plus chest X-ray, PFT plus HRCT, and PFT plus chest X-ray followed by HRCT). Patients were not eligible for this study if they had established IRD or were receiving immunosuppressive or antifibrotic treatment. All patients underwent pulmonary function testing and chest radiography. Patients with at least one suspicious finding in PFT (in case of DLCO < 80%) or chest X-ray (findings reported as suspicious for ILD by the radiologist) underwent pulmonary HRCT. This presents a potential limitation of this study as the diagnostic value of the algorithm could be potentially overestimated because HRCT was not performed on every patient in the study. Thus, for this PICO, we only present the findings of a sub-analysis in which all patients received HRCT.

Summary of Findings:

Overall, 63 (50%) of patients were identified as having ILD. Findings of the diagnostic tests indicated that reduced DLCO<80% and/or abnormal chest x-ray following by HRCT yielded the highest sensitivity and specificity in detecting ILD among patients with newly diagnosed IRD (Sensitivity: 89.5%, specificity: 65.8%). These findings suggest that the diagnostic accuracy of DLCO <80% plus HRCT is higher than DLCO <80% (or any other PFT) considered alone.

Table 9-1. Evidence for PICO 9: High-resolution CT thorax and PFTs compared to PFTs alone on diagnostic accuracy

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE rating
Critical outcome: Diagnostic accuracy						Very low[1]
Hoffman et al., 2022[1]	Case-control study	High ROB Unclear selection bias (uses elements if case control design); High blinding (blinding of test readers not reported); high verification (not all pts received HRCT)	63 IRD patients with ILD ILD patients Age: 53.8 % Female: 63% IRD: Connective tissue disease: 55.6% Vasculitis:24.4% Myositis: 19.0%	High resolution CT (HRCT) compared to pulmonary function tests (PFTs) PFTs include Diffusing capacity for carbon monoxide (DLCO), Forced expiratory volume in 1 s (FEV1), Forced vital capacity (FVC), Total lung capacity (TLC), Transfer factor of the lung for carbon monoxide (TLCO)	Diagnostic procedure parameter: AUC (95% CI) Cut-off for Sensitivity (SE), Specificity (SP), Positive likelihood ratio (LR+), Negative likelihood ratio (LR−) **Sub analysis of patients who received HRCT** (n=76; 38 with ILD and 38 without ILD) DLCO <80%: SE: 86.5%; SP: 36.1%, LR+ 1.35; LR-0.37 TLC <80%: SE: 32.7%; SP: 94.1%; LR+ 6.70; LR- 0,64 FVC <80%: SE: 55.6%; SP: 78.5%; LR+: 2.57; LR- 0.57 FEV1 <80% SE: 54.3%; SP: 78.4%; LR+ 2.51; LR- 0.58 TLCO <80%: SE: 60.0%; SP: 55.6%; LR+ 1.35; LR- 0.72 Chest X-ray: SE: 72.4%; SP: 58.6%; LR+ 1.75; LR- 0.47 HRCT: SE: 100%; SE: 52.6%; LR+ 2.11; LR- <0.001 DLCO + chest x-ray: SE: 89.5%; SP: 26.3%, LR+ 1.21; LR-0.40	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE rating
					PFT + Chest X-ray followed by HRCT if DLCO <80% or CXR abnormalities • **SE: 89.5%, SP: 65.8%, LR+ 2.62, LR- 0.16**	

[1]Certainty of evidence downgraded due to serious risk of bias, indirectness, and imprecision (single study with small sample)
AUC: area under the curve; **CI**: confidence intervals; **DLCO**: diffusing capacity for carbon monoxide; **FEV1:** forced expiratory volume in 1 s; FVC: forced vital capacity; **HRCT**: high-resolution computed tomography; **IRD:** inflammatory rheumatic diseases; **LR**: likelihood ratio; **PFT**: pulmonary function tests; **SE**: sensitivity: **SP**; specificity; **TLC**: total lung capacity; **TLCO**: transfer factor of the lung for carbon monoxide

Table 9-2. PICO 9 Excluded Studies

Reference	Reason for Exclusion
Abdelwahab et al., 2022[33]	Not a comparator of interest
Murdaca et al., 2021[24]	Not a comparator of interest
Carvalho et al., 2020[4]	Not a comparator of interest
Robles-Perez et al., 2020[27]	Not a comparator of interest
Bernstein et al., 2020[25]	Not a comparator of interest
Lucchino et al., 2020[16]	Not a comparator of interest
Guisado-Vasco et al., 2019[30]	Not a comparator of interest
Salaffi et al., 2019[14]	Not a comparator of interest
Manfredi et al., 2019[7]	Not a comparator of interest
Showalter et al., 2018[26]	Not a comparator of interest
Hax et al., 2017[5]	Not a comparator of interest
Roca et al., 2017[20]	Not a comparator of interest
Tashkin et al., 2017[17]	Not a comparator of interest
Suliman et al., 2015[28]	Not a comparator of interest
Frauenfelder et al., 2014[32]	Not a comparator of interest
Pernot et al., 2012[6]	Not a comparator of interest

Reference	Reason for Exclusion
Aubart et al., 2011[10]	Not a comparator of interest
Rosas et al., 2011[3]	Not a comparator of interest
Moghadam et al., 2011[2]	Not a comparator of interest
Morganroth et al., 2010[18]	Not a comparator of interest
Kostopoulos et al., 2008[23]	Not a comparator of interest
Fathi et al., 2008[19]	Not a comparator of interest
Lewszuk et al., 2008[12]	Not a comparator of interest
Camiciottoli et al., 2007[22]	Not a comparator of interest
Ayhan-Ardic et al., 2006[29]	Not a comparator of interest
Launay et al., 2006[11]	Not a comparator of interest
Bodolay et al., 2005[8]	Not a comparator of interest
Lee et al., 2005[15]	Not a comparator of interest
Clements et al., 2004[31]	Not a comparator of interest
Fathi et al., 2004[21]	Not a comparator of interest
Dawson et al., 2001[9]	Not a comparator of interest
McDonagh et al., 1994[13]	Not a comparator of interest

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7. Manfredi A, Cassone G, Cerri S, et al. Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the InSPIRAtE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device). *BMC pulmonary medicine*. 2019;19(1):111.
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PICO 10: In rheumatic disease patients at increased risk of developing ILD, what is the impact of bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) compared to no bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Indirect evidence from two case series studies suggests that bronchoalveolar lavage (BAL) used in patients with systemic sclerosis appears to be a safe procedure with no related hospitalizations and few adverse events and may aid in the diagnosis of ILD.

Summary:

Our searches identified two observational studies that provided indirect evidence on the use of bronchoalveolar lavage in patients with systemic sclerosis (SSc). *See Table 10-3 for additional resources to consider.*

Results from Observational Studies:

The findings of one study indicated that 50% of patients with SSc were identified as having alveolitis based on BAL findings (Silver et al., 1990[1]). Patients with alveolitis in this study had a more progressive course of their ILD (ΔFVC -0.69 L vs. -0.05 L, $p < 0.001$; ΔDLCO -2.94 mL/min/mmHg vs. 0.16 mL/min/mmHg, $p=0.03$; over 1.9 and 1.47 years respectively). The authors reported that BAL was used to select patients with alveolitis and at risk of pulmonary deterioration, and treatment was instituted with cyclophosphamide and prednisone, resulting in significant improvement in dyspnea ($p<0.001$). Thus, BAL demonstrated value in identifying patients with ILD. The other study indicated that BAL identified 9 of the 18 patients followed in the study as having active alveolitis recorded in both the middle and lingual lobe segments, while in 4 patients, it was recorded in only one segment (lower lobe in 3) (Clements et al., 2004[2]). For the right middle lung lobe or lingula, there was excellent agreement between ground-glass opacification and the finding of alveolitis on BAL from segments in the same lung regions, but this was not observed for the lower lobes. The findings of the study further demonstrated BAL to be a safe modality with no hospitalizations and only one episode of bronchospasm.

The literature reviewer for this PICO question notes that both studies were written prior to the standardization of the nomenclature that we use to discuss interstitial lung diseases. BAL represents an outdated diagnostic technique, previously used to aid in diagnosis and prognosis in patients with a rheumatic disease (Wallaert B, et al.,1990[3]).

There were no trials examining the use of transbronchial biopsy (TBBx) or cryobiopsy (TBLC) in the population of interest to this PICO (i.e., patients with rheumatic diseases). However, there are well-described rates of diagnosis and adverse events in a broader interstitial lung disease population (Kebbe et al., 2017[4]). In one retrospective cohort study that included one patient with collagen vascular disease, TBBx was correlated with the ultimate diagnosis of ILD with a sensitivity of 58.8% and specificity of 100% (Fend et al., 1989[5]). However, diagnostic rates vary by type of interstitial lung disease. Adverse events associated with TBBx include a low rate of bleeding (1–4%) and pneumothorax (1–6%).[4] The use of TBLC in the rheumatic disease patient is also not specifically described. A prospective cohort trial comparing TBLC to surgical lung biopsy (the COLDICE study) specifically excluded patients with collagen vascular disease (Troy et al., 2020[6]). The major adverse events associated with TBLC include mortality (0.3–0.7%), pneumothorax (20–22%), and bleeding (0–78%).

Table 10-1. Evidence for PICO 10: Bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) compared to no bronchoscopy

Author, year	Study design	Risk of bias	Follow-up	Population Description	Screening or assessment measures	Results	GRADE rating
Critical outcome: adverse event							Very low[1]
Clements et al., 2004[2]	Retrospective case series	High, small study, selection bias, measurement bias	Not reported	18 patients with systemic sclerosis (SSc) and dyspnea Age: 51 years % Female: 66% Duration of disease: 1.5 years	Bronchoalveolar lavage (BAL) Patients evaluated for ILD by pulmonary function testing (PFTs) and BAL, and 15 of these patients underwent chest high resolution computed tomography (HRCT). BAL was performed in either the middle lobe or the lingula, and in a lower lung segment.	● **Critical outcome: adverse events:** Following the BAL procedure 0/18 patients required hospitalization, and 1/18 had a complication (bronchospasm). ● Nine of the 18 patients had active alveolitis recorded in both the middle and lingual lobe segments, while in 4 patients it was recorded in only 1 segment (lower lobe in 3). ● For the right middle lung lobe or lingula there was excellent agreement between ground-glass opacification and the finding of alveolitis on BAL from segments in the same lung regions, but this was not observed for the lower lobes.	
Silver et al., 1990[1]	Retrospective case series	High, small study, selection bias, measurement bias	Not reported	43 patients with systemic sclerosis (SSc) Age: 43.9 years % Female: 60%	Bronchoalveolar lavage (BAL) Results compared to 14 normal controls	**No critical outcomes reported** ● Patients with abnormal BAL cell count (compared with controls) had significantly greater deterioration in PFT over time (ΔFVC -0.69 L vs -0.05 L, p <0.001; ΔDLCO -2.94 mL/min/mmHg vs +0.16	

Author, year	Study design	Risk of bias	Follow-up	Population Description	Screening or assessment measures	Results	GRADE rating
				Disease duration: 4.6 years		mL/min/mmHg, p=0.03; over 1.9 and 1.47 years respectively). ● 50% of patients with SSc were identified as having alveolitis based on BAL findings. ● BAL was used to select patients with alveolitis and at risk of pulmonary deterioration, and treatment was instituted with cyclophosphamide and prednisone, resulting in significant improvement in dyspnea (p<0.001)	

[1]Certainty of evidence rated low due to serious risk of bias and indirectness

Table 10-2. PICO 10 Exclude Studies

Reference	Reason for exclusion
Tomassetti et al., 2022[7]	Population not of interest
Troy et al., 2020[6]	Population not of interest
Mohamed et al., 2013[8]	Population not of interest
Komocsi et al., 2001[9]	Not a comparator of interest
Witt et al., 1996[10]	No outcome of interest
Fend et al., 1989[5]	Population not of interest

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Table 10-3. Additional Resources to Consider

Reference	Notes
Additional considerations from Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST	Diagnostic yield: Diagnostic yield. Diagnostic yield was defined as the number of procedures that yielded a histopathological diagnosis divided by the total number of procedures performed. The diagnostic yield of Transbronchial lung cryobiopsy (TBLC) in patients with ILD of undetermined type was 79% (28, 31–38, 40, 41, 44–47, 50–52, 54, 55, 57, 58, 60–63, 65, 66, 68). There was no difference in diagnostic yield across subgroups related to publication date, study size, or cryoprobe size. Only sample number appeared to affect diagnostic yield, with a diagnostic yield of 85% when three or more samples were collected (28, 33, 38, 44, 45, 51, 55, 63, 66, 69) and a diagnostic yield of 77% or less when fewer samples were collected. Diagnostic agreement: Two studies reported agreement between the diagnostic interpretation of TBLC samples and surgical lung biospy (SLB samples) (28, 60). The larger study demonstrated 70.8% agreement, which increased to 76.9% diagnostic agreement after MDD (28). Post hoc analysis suggested that agreement of TBLC with SLB improves by taking more samples (29). In contrast, the smaller study reported diagnostic agreement of only 38% (60). Complications of TBLC included pneumothorax in 9% (28, 31, 33–35, 37, 39–43, 46, 48–50, 53–55, 60, 63, 68, 69) and any bleeding in 30% (28, 31, 33, 36, 39, 47, 50, 51, 55, 67–69). Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare.

PICO 11: In rheumatic disease patients at increased risk of developing ILD, what is the impact of surgical lung biopsy compared to no surgical lung biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective observational study[1] provided direct evidence that surgical lung biopsy and transbronchial lung cryobiopsy had similar results in the percentage of cases in which management strategies changed (38% and 31%, respectively), but notably, this study was almost entirely patients with suspected ILD who did not have autoimmune rheumatic disease.

Summary:

Our searches identified one observational study that provided indirect evidence on the value of lung biopsy in diagnosing and managing ILD (Tomassetti et al., 2022[1]). The study enrolled very few patients with rheumatic disease and did not directly assess the diagnostic accuracy of ILD with or without biopsy. Instead, it considered the value of biopsy in managing patients with biopsy-detected ILD. *See additional resources to consider in Table 11-3.*

Results from the observational study:

Biopsy results reported in the study indicated that 189 patients suspected of ILD had idiopathic pulmonary fibrosis (IPF), 143 had non-IPF fibrotic ILDs, and 94 had nonfibrotic ILDs. Two of the patients with ILD had connective tissue disease. Lung biopsy data changed the management strategy in 145 cases (34%), with similar results for transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy (SLB, the treatment strategy changed in 31.5% of TBLC cases, 84/266, P=0.001, and in 38% of SLB, 61/160, P=0.001). After lung biopsy, the treatment team was less inclined to "wait and see" (from 15% to 4% of cases, P<0.001) or to prescribe steroids only (from 54% to 37%, P <0.001) and was more confident to treat with antifibrotics (from 23% to 44%, P<0.001) or immunosuppressive drugs (from 7% to 14%, P <0.001).

Surgical lung biopsy has been shown in large databases to have significant mortality of around 1.7% which has led many pulmonologists and surgeons to prefer using alternative modalities for the diagnosis of interstitial lung disease.[2] However, in appropriate cases, more tissue may be needed to make a diagnosis. In the case of patients with rheumatic disease, many times an etiology for interstitial lung disease is already known and subjecting a patient to the potential harm of a surgical lung biopsy is not needed.

Table 11-1. Evidence for PICO 11: Surgical lung biopsy compared to no surgical lung biopsy

Author, year	Study design	Risk of bias	Time of reassessment	Population Description	Screening or assessment measures	Results	GRADE Rating
Tomassetti et al., 2022[1] To evaluate lung biopsy findings on patient management decisions	Retrospective cohort study	High, selection bias, measurement bias (test readers not blinded), very few patients with ARD	Not reported	426 patients with suspected ILD of which 2 had connective tissue disease	Patients evaluated with transbronchial lung cryobiopsy (TBLC, n=266) or surgical lung biopsy (SLB, n=160)	**No critical outcomes reported** ● 189 idiopathic pulmonary fibrosis (IPF), 143 non-IPF fibrotic ILDs, and 94 nonfibrotic ILDs ● Lung biopsy data changed the management strategy in 145 cases (34%), with similar results for TBLC and SLB (the treatment strategy changed in 31.5% of TBLC cases, 84/266, P=0.001, and in 38% of SLB, 61/160, P=0.001) ● After lung biopsy, the treatment team was less inclined to "wait and see" (from 15% to 4% of cases, P<0.001) or to prescribe steroids only (from 54% to 37%, P <0.001) and was more confident to treat with antifibrotics (from 23% to 44%, P<0.001) or immunosuppressive drugs (from 7% to 14%, P <0.001).	Very low *Indirect evidence

Table 11-2. PICO 11 Excluded Studies

Reference	Reason for exclusion
Troy et al., 2020[4]	Population not of interest
Burge et al., 2017[3]	Does not address PICO
Parambil et al., 2006[5]	No outcomes of interest
Lee et al., 2005[6]	No outcomes of interest
Fend et al., 1989[7]	Population not of interest

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7. Fend F, Mikuz G, Ott G, Rothmund J. Diagnostic value of combined bronchoalveolar lavage and transbronchial lung biopsy. *Pathology Research and Practice*. 1989;184(3):312-317.

Table 11-3. Additional Resources to Consider

Reference	Notes
Additional considerations from Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST	Diagnostic yield: Diagnostic yield. Diagnostic yield was defined as the number of procedures that yielded a histopathological diagnosis divided by the total number of procedures performed. The diagnostic yield of Transbronchial lung cryobiopsy (TBLC) in patients with ILD of undetermined type was 79% (28, 31–38, 40, 41, 44–47, 50–52, 54, 55, 57, 58, 60–63, 65, 66, 68). There was no difference in diagnostic yield across subgroups related to publication date, study size, or cryoprobe size. Only sample number appeared to affect diagnostic yield, with a diagnostic yield of 85% when three or more samples were collected (28, 33, 38, 44, 45, 51, 55, 63, 66, 69) and a diagnostic yield of 77% or less when fewer samples were collected. Diagnostic agreement: Two studies reported agreement between the diagnostic interpretation of TBLC samples and surgical lung biospy (SLB samples) (28, 60). The larger study demonstrated 70.8% agreement, which increased to 76.9% diagnostic agreement after MDD (28). Post hoc analysis suggested that agreement of TBLC with SLB improves by taking more samples (29). In contrast, the smaller study reported diagnostic agreement of only 38% (60). Complications of TBLC included pneumothorax in 9% (28, 31, 33–35, 37, 39–43, 46, 48–50, 53–55, 60, 63, 68, 69) and any bleeding in 30% (28, 31, 33, 36, 39, 47, 50, 51, 55, 67–69). Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare.

PICO 12: In rheumatic disease patients with ILD, what is the impact of pulmonary function tests (PFTs) compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Additional consideration: Consider pulmonary function testing and the 6-minute-walk test every 4–6 months or sooner if clinically indicated.

Table 12-1. PICO 12: Excluded Studies

Reference	Reason for exclusion
Solomon et al., 2022[17]	Not a comparator of interest
Chen et al., 2022[16]	No outcomes of interest
Raghu et al., 2022[10]	Not a comparator of interest
Xu et al., 2020[24]	Not a comparator of interest
Narvaez et al., 2020[18]	Not a comparator of interest
Nawata et al., 2020[7]	Not a comparator of interest
Hoa et al., 2019[1]	Not a comparator of interest
Volkmann et al., 2019[26]	Not a comparator of interest
Fu et al., 2019[25]	Not a comparator of interest
Occhipinti et al., 2019[14]	Not a comparator of interest
Kafaja et al., 2018[20]	No outcomes of interest
Rojas-Serrano et al., 2017[23]	Not a comparator of interest
Okamoto et al., 2016[21]	Not a comparator of interest
Tashkin et al., 2016[19]	No outcomes of interest
Kloth et al., 2016[15]	Not a comparator of interest
Moore et al., 2015[13]	Not a comparator of interest
Rojas-Serrano et al., 2015[12]	Not a comparator of interest

Reference	Reason for exclusion
Mira-Avendano et al., 2013[22]	Not a comparator of interest
Volpinari et al., 2011[6]	Not a comparator of interest
DeSantis et al., 2010[4]	Not a comparator of interest
Colaci et al., 2010[2]	Not a comparator of interest
Tille-Leblond et al., 2008[11]	No outcomes of interest
Goldin et al., 2008[9]	Not a comparator of interest
Strange et al., 2008[3]	Not a comparator of interest
Bodolay et al., 2005[8]	No outcomes of interest.
Behr et al., 1996[5]	Not a comparator of interest

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Table 12-2. Additional Resources to Consider

Reference	Notes
Additional considerations from Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST	Diagnostic yield: Diagnostic yield. Diagnostic yield was defined as the number of procedures that yielded a histopathological diagnosis divided by the total number of procedures performed. The diagnostic yield of Transbronchial lung cryobiopsy (TBLC) in patients with ILD of undetermined type was 79% (28, 31–38, 40, 41, 44–47, 50–52, 54, 55, 57, 58, 60–63, 65, 66, 68). There was no difference in diagnostic yield across subgroups related to publication date, study size, or cryoprobe size. Only sample number appeared to affect diagnostic yield, with a diagnostic yield of 85% when three or more samples were collected (28, 33, 38, 44, 45, 51, 55, 63, 66, 69) and a diagnostic yield of 77% or less when fewer samples were collected. Diagnostic agreement: Two studies reported agreement between the diagnostic interpretation of TBLC samples and surgical lung biospy (SLB samples) (28, 60). The larger study demonstrated 70.8% agreement, which increased to 76.9% diagnostic agreement after MDD (28). Post hoc analysis suggested that agreement of TBLC with SLB improves by taking more samples (29). In contrast, the smaller study reported diagnostic agreement of only 38% (60). Complications of TBLC included pneumothorax in 9% (28, 31, 33–35, 37, 39–43, 46, 48–50, 53–55, 60, 63, 68, 69) and any bleeding in 30% (28, 31, 33, 36, 39, 47, 50, 51, 55, 67–69).

	Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare.

PICO 13: In rheumatic disease patients with ILD, what is the impact of high-resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Indirect findings from four observational studies suggest that a combination of pulmonary function tests (PFTs), symptoms, and high-resolution computed tomography (HRCT) may be more helpful in monitoring ILD progression compared to any test used alone.
- No studies addressed the impact of HRCT compared to or in addition to history and physical on responsiveness/sensitivity to change in test, treatment-related serious adverse events, or testing-related adverse events.

Additional consideration: Consider annual HRCT if there is clinical suspicion of worsening or risk of lung cancer

Summary of Evidence:

Two posthoc analyses of data from the Scleroderma Lung Study I and II (Kim H., et al., 2011,[1] Kim H., et al., 2020[2]), and two other observational studies provided indirect evidence to address this PICO (Roca, F. et al., 2017,[3] Tardella, M. et al., 2022[4]).

Results from Post-hoc analysis of data from Scleroderma Lung Study I and II (SLS I and II):

Data from SLS I provided indirect evidence that HRCT may be more helpful than history and physical alone in assessing treatment effect in 98 symptomatic systemic sclerosis (SSc)-ILD patients treated with cyclophosphamide versus placebo (Kim H., et al., 2011[1]). In this study, there were weak correlations between changes in quantitative lung fibrosis as measured by HRCT and dyspnea score with treatment, suggesting that combined measures may be helpful in monitoring treatment effect. Data from SLS II indicated that in 97 SSc-ILD patients treated with cyclophosphamide versus MMF, there was some improvement in transition from fibrosis and ground glass pattern to normal pattern on HRCT in both arms; also, less baseline dyspnea was associated with improvement from ground glass to normal lung pattern in both treatment arms (Kim H., et al, 2020[2])

Results from observational studies:

Roca, F. et al., 2017[3] compared ILD progression among a subset of 21 patients with Sjogren's syndrome and detected ILD. Progression was based on those who deteriorated, remained stable, or improved based on findings from PFTs, symptoms, and HRCT findings. Overall, 7 patients with ILD deteriorated and 12 stabilized/improved. Among those who deteriorated, DLCO was significantly lower at the last PFT assessment (24 months). No differences were observed in symptoms (cough/dyspnea), HRCT appearance, or other presenting PFTs among those who progressed compared to those who remained stable or improved. These findings suggest that neither HRCT nor history and physical alone may be particularly helpful for risk stratifying based on anticipated disease outcomes. Tardella, M. et al., 2022[4] evaluated 75 patients with rheumatoid arthritis (RA) and ILD receiving abatacept (n=31) versus JAK-inhibitors (n=44) and found that Borg dyspnea index changed significantly from baseline to 18 months in both treatment groups, but HRCT evaluated with computer-aided method did not differ significantly in the two groups from baseline to 18 months.

Table 13-1. Evidence for PICO 13: High-resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation)

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
Findings from Post-hos analysis of Scleroderma Lung Study I and II							
Kim et al., 2020[2] Date from Scleroderma Lung Study II (SLS) Using HRCT to measure patterns of ILD in response to immunosuppressive therapy of systemic sclerosis-related ILD (SSc-ILD)	Post-hoc of randomized controlled trial	High, selection bias, measurement variation, no validation by histopathology.	Mean duration between baseline and follow-up CT scan was 24.6 (+/-1.9) months	97 patients with symptomatic SSc-ILD; 47 received CYC and 50 received MMF Age: 52 years % Female: 72% mean FVC at baseline: 66.3%, mean DLCO at baseline: 55%	Evaluated various changes in CT from baseline to follow-up in each of the treatment arms and between stable, improved, and worsened groups.	● During treatment, there was no significant change in transitional probabilities of ILD patterns between two treatment arms based on HRCT. ● There was mean net improvement in transitions from both lung fibrosis and ground glass to a normal pattern in both treatment arms, but essentially no significant net improvement in transitions from lung fibrosis to ground glass. ● Less baseline dyspnea was associated with improvement in ground glass to normal pattern.	Very low **No critical outcomes reported**

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
						• Better FVC and worse skin score were associated with favorable transitions from lung fibrosis patterns to normal lung. • Findings inconclusive if HRCT is sufficient for monitoring treatment efficacy.	
Kim et al., 2011[1] Date from Scleroderma Lung Study I (SLS) Purpose: to determine if quantitative lung fibrosis scores obtained through HRCT can provide a quantitative tool for assessing treatment efficacy.	Post-hoc of randomized controlled trial	High, selection bias, potential measurement error	12 months	98 patients with systemic sclerosis (SSc-ILD) from SLS I study who had digital HRCT images at baseline and 12 months. 41 patients got cyclophosphamide and 42 got placebo	Images from high-resolution computed tomography (HRCT) were quantified into quantitative lung fibrosis (QLF) scores using changes in texture that quantify lung fibrosis Comparisons were made to pulmonary function tests (PFTs) and dyspnea score to establish associations.	Findings based on the most severe zone (covering the chest into upper, middle, and lower zones) identified at baseline and the whole chest. 12 months follow-up QLF scores decreased by 2.6% in the cyclophosphamide group, whereas they increased by 9.1% in the placebo group, leading to ~12% difference (p=0.0027). Between-treatment difference in whole lung QLF was ~5% (p=0.0190)	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
						Significant associations were observed between changes in QLF and FVC (r=−0.33), dyspnea score (r=−0.29), and consensus visual score of lung fibrosis (p=0.001). The correlation coefficients were far away from 0 suggesting combination of measures and evaluations are more helpful for monitoring.	
Findings of Other Observational Studies							
Roca et al., 2017[3]	Retrospective cohort study	High, very small study (small number of patients with ILD), significant heterogeneity in HRCT scans.	Initial assessment and median follow-up of ILD patients was 24 months	263 patients with primary Sjogren's syndrome, 21 of those with ILD. ILD patients consisted of 3 men and 21 women.	PFT: vital capacity (VC), forced VC (FVC), and diffusing capacity for carbon monoxide (DLCO). HRCT scan was performed to evaluate abnormalities consistent with ILD, i.e.: parenchymal micronodules/nodules, irregular linear opacities, irregularity of the interfaces between peripheral pleura and aerated lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectasis or bronchiectasis].	7 patients with ILD deteriorated, 12 stabilized/improved. Among those who deteriorated, DLCO was significantly lower at last PFT assessment. No difference in symptoms (cough/dyspnea), HRCT appearance, or presenting PFTs. **Pulmonary characteristics** **Cough:** Deteriorated: 5 (71.4%); Improved: 7 (58.3%), p= 0.67 **Dyspnea:** Deteriorated: 6 (85.7%); Improved: 6 (50%), p= 0.17 **HRCT scan pattern**	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
					HRCT pattern has been correlated with pulmonary histological findings, i.e.: 1) cryptogenic organizing pneumonia (COP) is mainly characterized by consolidation and linear opacities; 2) nonspecific interstitial pneumonia (NSIP) is principally defined by ground-glass opacities and irregular linear opacities; 3) usual interstitial pneumonia (UIP) is mainly characterized by honeycombing and traction bronchiectasis; and 4) lymphoid interstitial pneumonia (LIP) is principally defined by centrolobular and subpleural nodes, cysts and ground-glass opacities.	**NSIP**: Deteriorated: 3 (42.9%); Improved: 4 (33.3%) **UIP**: Deteriorated: 3 (42.9%); Improved: 2 (16.7%) **COP**: Deteriorated: 0 (0%); Improved: 2 (16.7%) **LIP:** Deteriorated: 0 (0%); Improved: 2 (16.7%) / **Undetermined:** Deteriorated: 1 (14.3%); Improved: 2 (16.7%) **PFTs at last follow-up** **VC (%):** Deteriorated: 85%, range: 44–126; Improved 113%, range: 83–154, p= 0.15 **FVC (%):** Deteriorated: 78%, range: 45–135; Improved: 116%, range: 85–150, p= 0.11 **DLCO (%):** Deteriorated: 47%, range: 14-65; 64%, range:54–88, p= 0.048 **Mortality:** Deteriorated: 1% (14.3); Improved: 1% (8.3), p=1.0	
Tardella et al., 2022[4]	Retrospective cohort study	High, small study, selection bias due largely to	18 months of therapy	75 patients with RA-ILD receiving abatacept (ABA, 31 patients) or	HRCT, FVC and DLCO, Borg's dyspnea index.	In ABA group, 11% patients showed HRCT deterioration, 73% were	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
		non-randomized, retrospective nature of study		Janus-kinase (JAK) inhibitors (44 patients)		stable, 16% improved on HRCT. In JAK group, 16% deteriorated, 64% were stable, 19% improved on HRCT. Borg dyspnea index was significantly different from baseline to 18 months in both groups DLCO, FVC, HRCT-CaM fibrosis changes were not significantly different from baseline to 18 months in both groups. HRCT helpful in addition to PFTs. Unclear if helpful in addition to history/physical. **Borg Dyspnea Index**: ABA: Time 0 (T0): 2.54±1.23; (T18) 1.90±1.01, p<0.01 JAK: T0: 0.01 2.51±1.22; T18 1.87±1.11, p= 0.03 **DLco (% predicted)** ABA T0: 58.69±8.24; T18: 61.26±11.23, p= 0.22	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/Comparator	Results	GRADE rating
						JAK T0: 59.72±8.56; T18: 62.75±11.84, p=0.28 **FVC (% predicted)** ABA T0: 82.29±4.86; T18: 81.24±11.97, p=0.59 JAK: T0: 81.18±5.07; T18: 79.59±14.02, p= 0.55 **HRCT-CaM fbrosis (%)** ABA T0: 19.41±5.89; T18: 18.94±6.06, p= 0.71 JAK: T0:18.54±6.31, T18: 17.52±6.35, p= 0.53	

Table 13-2. PICO 13: Excluded Studies

Reference	Reason for exclusion
Wu et al., 2022[9]	Not a comparator of interest
Soloman et al., 2022[22]	No intervention of interest
Raghu et al., 2022[26]	Wrong study design
Yang et al., 2021[11]	Does not address PICO
Tyker et al., 2021[19]	Not a comparator of interest
Cronin et al., 2021[15]	Not a comparator of interest
Xu et al., 2020[27]	Does not address PICO
Narvaez et al., 2020[23]	Not a comparator of interest
Kafaja et al., 2018[24]	No intervention of interest
Sanges et al., 2017[5]	No comparator or outcome of interest.
Ariani et al., 2017[14]	Not a comparator of interest
Ariani et al., 2017[14]	Not a comparator of interest

Reference	Reason for exclusion
Kim et al., 2016[16]	Not a comparator of interest
Moore et al., 2015[21]	Not a comparator of interest
Ikeda et al., 2015[12]	No outcomes of interest
Mira-Avendano et al., 2013[25]	Not a comparator of interest
Volpinari et al., 2011[18]	Not a comparator of interest
Tanizawa et al., 2011[10]	Not a comparator of interest
DeSantis et al., 2010[7]	Does not address PICO
Tille-Leblond et al., 2008[28]	Does not address PICO
Strange et al., 2008[6]	Does not address PICO
Camiciottoli et al., 2007[20]	No outcomes of interest
Bodolay et al. 2005[8]	Not a comparator of interest
Schnabel et al. 2003[13]	Not a comparator of interest
Behr et al. 1996[17]	Not a comparator of interest

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2. Kim GHJ, Tashkin DP, Lo P, et al. Using Transitional Changes on High-Resolution Computed Tomography to Monitor the Impact of Cyclophosphamide or Mycophenolate Mofetil on Systemic Sclerosis-Related Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(2):316-325.
3. Roca F, Dominique S, Schmidt J, et al. Interstitial lung disease in primary Sjogren's syndrome. *Autoimmunity reviews*. 2017;16(1):48-54.
4. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712.
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12. Ikeda S, Arita M, Morita M, et al. Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: to lump or split? *BMC pulmonary medicine*. 2015;15:159.
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PICO 14: In rheumatic disease patients with ILD, what is the impact of 6-minute walk test distance compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Additional consideration: Consider pulmonary function testing and the 6-minute-walk test every 4–6 months or sooner if clinically indicated

Table 14-1. PICO 14: Excluded Studies

Reference	Reason for exclusion
Sanges et al., 2017[1]	No comparator or outcome of interest.

References

1. Sanges S, Giovannelli J, Sobanski V, et al. Factors associated with the 6-minute walk distance in patients with systemic sclerosis. *Arthritis research & therapy*. 2017;19(1):279.

PICO 15: In rheumatic disease patients with ILD, what is the impact of chest radiograph compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse event?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 15-1. PICO 15: Excluded Studies

Reference	Reason for exclusion
Padley et al., 1991[1]	Population not of interest

References

1. Padley SPG, Hansell DM, Flower CDR, Jennings P. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clinical Radiology*. 1991;44(4):222-226.

PICO 16: In rheumatic disease patients with ILD, what is the impact ambulatory desaturation compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physician examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 17: In rheumatic disease patients with ILD, what is the impact of chest radiograph compared to high resolution CT thorax on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 17-1. PICO 17: Excluded Studies

Reference	Reason for exclusion
Tomassetti et al., 2022[2]	Population and intervention not of interest
Padley et al., 1991[1]	Population not of interest

References

1. Padley SPG, Hansell DM, Flower CDR, Jennings P. Comparative accuracy of high-resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clinical Radiology*. 1991;44(4):222-226.
2. Tomassetti S, Ravaglia C, Puglisi S, et al. Impact of Lung Biopsy Information on Treatment Strategy of Patients with Interstitial Lung Diseases. *Annals of the American Thoracic Society*. 2022;19(5):737-745.

PICO 18: In rheumatic disease patients with ILD, what is the impact of bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) compared to no bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 18-1.PICO 18: Excluded Studies

Reference	Reason for exclusion
Tomassetti et al., 2022[7]	Not a comparator of interest
He, L. et al., 2022[5]	Not a comparator of interest
Ikeda et al., 2015[9]	Not a comparator of interest
DeSantis et al., 2012[3]	Not a comparator of interest
Colaci et al., 2010[1]	Not a comparator of interest
Tille-LeBlond et al., 2008[8]	Not a comparator of interest
Goldin et al., 2008[6]	Not a comparator of interest
Strange et al., 2008[2]	Not a comparator of interest
Parambil et al., 2006[10]	Not a comparator of interest
Behr et al., 1996[4]	Not a comparator of interest

References

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8. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.
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PICO 19: In rheumatic disease patients with ILD, what is the impact of high-resolution CT thorax compared to bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- There is some evidence that bronchoscopy may aid in the evaluation of the risk of ILD progression defined radiographically by increase in honeycombing, but this was not associated with functional decline as measured by PFT. Baseline HRCT evidence of ILD was similarly associated with worsening in honeycombing at follow-up, and thus the additional value of BAL over HRCT is unclear.
    - Persistence of alveolitis (as measured by bronchoalveolar lavage [BAL]) at 1-year post-treatment with cyclophosphamide was associated with worsening in FVC and DLCO in almost half of the patients with systemic sclerosis (n=5/12). Normalization of alveolitis post-treatment with cyclophosphamide was associated with stabilization of FVC and DLCO in most patients one-year post-treatment (n=8/11) (Colaci M et al., 2010[1]).
    - Radiographic worsening was seen more commonly in patients with persistent alveolitis at the end of CYC treatment (mean 21.1 +/- 8.9 months) than those with normalization (n=8/12 vs. n=1/11, respectively) (Colaci M et al., 2010[1]).
    - Baseline alveolitis on BAL fluid and the presence of ILD on baseline high-resolution computed tomography (HRCT) were associated with worsening honeycombing at one-year follow-up (DeSantis M et al., 2012[2]). Neither baseline alveolitis nor baseline ILD on HRCT was associated with worsening in ground glass opacities (GGO) on HRCT, worsening FVC on PFT, or worsening DLCO at one-year follow-up.

Summary:

Our searches identified two observational studies that indirectly addressed this PICO question (Colaci M et al., 2010,[1] DeSantis M, et al., 2012[2]). Neither study directly assessed the impact of HRCT compared to bronchoscopy on outcomes of interest, but each provided evidence to indirectly evaluate this question and was thus included.

Results from Observational Studies:

The study by Colaci M. et al., 2010[1] examined the association between improvement in alveolitis (as measured by bronchoalveolar lavage [BAL]) after cyclophosphamide treatment and associated changes in pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT). Persistent alveolitis on repeat BAL fluid at the end of CYC treatment was associated with stable FVC and DLCO but worsening in FVC and DLCO at 1-year post-treatment in almost half of the patients (n=5/12). On the contrary, normalization of BAL fluid at the end of CYC was associated with improvement or stabilization in FVC and DLCO and worsening in only 2/11 at one-year post-treatment. Radiographic worsening was seen more commonly in patients with persistent alveolitis at the end of CYC treatment than in those with normalization (n=8/12 vs. n=1/11, respectively). The study did not report on whether radiographic worsening was associated with worsening in FVC and/or DLCO. Therefore, direct comparisons between the impact of serial HRCT vs. BAL on monitoring outcomes could not be directly assessed.

The study by DeSantis et al., 2012[2] reported that ILD on baseline HRCT (regardless of alveolitis on baseline BAL) was associated with worsening in the honeycombing score at follow-up ($p<0.0001$) compared with no ILD at baseline HRCT, but not worsening in ground glass opacity score on HRCT, worsening in FVC, or worsening at one-year follow-up. Alveolitis on BAL at baseline was associated with worsening in the honeycombing score at one-year follow-up HRCT ($p<0.01$), but not worsening in alveolitis (GGO) score on HRCT, worsening in FVC, or worsening in DLCO. Repeat BAL at one year was not performed, limiting comparisons on the impact of change in alveolitis on outcomes of interest. At the 36-month follow-up, nine patients died, most of whom had alveolitis at baseline (78%). The percentage of neutrophils was associated with mortality on univariate, but not multivariable analysis. Thus, the association between alveolitis and mortality is potentially insignificant. Honeycombing score on baseline HRCT scan was associated with mortality on multivariable Cox analysis; however, variables included in the model were not clearly stated; thus, conclusions were limited. Overall, there is some evidence that bronchoscopy may aid in the evaluation of the risk of ILD progression defined radiographically by an increase in honeycombing, but this was not associated with functional decline as measured by PFT. Baseline HRCT evidence of ILD was similarly associated with worsening in honeycombing at follow-up, and thus the additional value of BAL over HRCT is unclear.

Table 19-1. Evidence for PICO 19: High-resolution CT thorax compared to bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy)

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
Colaci et al., 2010[1]	Retrospective cohort study	High risk of bias, small study with selection bias and lack of blinding of outcome assessors	26 patients with systemic sclerosis (SSc) and alveolitis on baseline bronchoalveolar lavage (BAL) and ILD on baseline high resolution computed tomography (HRCT) Age (y, mean, +/- SD): 47.8 ± 10.5 % Female: 76%	Diagnostic and prognostic tests: BAL, HRCT, and pulmonary function tests (PFTs) Outcome (definition of "worsening"): ● FVC change >10% ● DLCO change >15% ● Appearance/ disappearance of fibrotic areas on HRCT Timepoints ● End of cyclophosphamide (CYC) treatment (mean 21.1 +/- 8.9 months) ● One-year post-CYC	**End of CYC therapy** ● BAL fluid normalized in 12/26 (46.2%) (group 1) ● BAL fluid remained abnormal in 14/26 (53.8%) (group 2) ● Normalization of BAL fluid (group 1) at end of CYC associated with clinical improvement or stabilization in FVC and/or DLCO ● Persistent alveolitis on BALF at end of CYC therapy associated with stabilization of FVC and/or DLCO at end CYC treatment ● Lack of correlation between HRCT and BALF at baseline and post CYC therapy **One year post CYC therapy** ● In group with improved BAL fluid end of CYC therapy (n=11), 2/11 had worsening FVC and DLCO at one year post CYC therapy with others stable ● In group without improvement in BAL fluid end of CYC therapy, 5/12 patients had worsening FVC and/or DLCO ● Fisher's exact test between two groups not significant (p=ns)	Very low No critical outcomes reported

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					• Radiographic worsening in ILD was seen in 1/11 subjects in group 1 (normalization of BAL fluid group) versus 8/12 in group 2 (persistent alveolitis group) • Worsening of HRCT scan was not evaluated on the outcome of FVC and/or DLCO worsening	
DeSantis et al., 2010[2]	Prospective Cohort study	High risk of bias; selection bias, measurement bias	110 systemic scleroses (SSc): 73 with evidence of ILD on HRCT underwent BAL Age (y, mean, +/- SD): *Total cohort* 54.9 ± 12.6 *BAL* 55.6 ± 12.8 % Female: *Total cohort* 96 (87.3%) *BAL* 62 (84.9%)	Dx: PFTs, HRCT, BAL (alveolitis diagnosed if neutrophils >=3% and/or eosinophils >=2% Outcomes: Change PFT and HRCT, Mortality Time: 1-year follow-up; survival at 36 mo. PFTs include Diffusing capacity for carbon monoxide (DLCO) (unknown if corrected for Hgb), Forced expiratory volume in 1 s (FEV1), Forced vital capacity (FVC), Total lung capacity (TLC) HRCT ILD scored by two independent readers; scored GGO ("alveolar score") and honeycombing in 3 lobes of each lung, scoring severity on scale of 0-5. Increase in alveolar or honeycombing	**1 year follow-up** **Patients with ILD on HCRT at baseline** • Worsening of alveolar (GGO) score: 35/73 (47.9%) • Worsening in honeycombing score: 27/73 (37.0%) • Worsening in FVC: 10/73 (13.7%) • Worsening in DLCO: 23/73 (31.5%) **Pts with alveolitis on BAL at baseline** • Worsening alveolar (GGO) score: 19/37 (51.4%) • Worsening honeycombing score: 19/37 (51.4%), p=0.003 • >10% decrease FVC: 4/37 (10.8%) • >15% decrease DLCO: 11/37 (29.8%) **Patients without alveolitis on BAL on baseline** • Worsening alveolar (GGO) score: 16/36 (44.4%)	Very low No critical outcomes reported

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
				score >1 considered clinically significant	• Worsening honeycombing score: 8/36 (22.2%), p=0.025 • >10% decrease FVC: 6/36 (16.7%) • >15% decrease DLCO: 12/36 (33.3%) ILD at baseline HRCT (regardless of BAL alveolitis) associated with worsening in honeycombing score at follow-up (p<0.0001) compared with no ILD at baseline HRCT, but not worsening in alveolitis (GGO) score HRCT, worsening in FVC, or worsening in DLCO Alveolitis on BAL at baseline associated with worsening in honeycombing score at follow-up (p<0.01), but not worsening in alveolitis (GGO) score HRCT, worsening in FVC, or worsening in DLCO *No significant differences in worsening alveolitis GGO score HRCT, worsening honeycombing score, worsening FVC, worsening DLCO in treated vs. untreated patients at 1-year follow-up <u>Survival at 36 months</u> • 9 patients died (all with ILD); 7 (77.8%) patients had alveolitis on BAL at baseline. • Baseline DLCO (p<0.0001), PAH (0.033), and BAL neutrophil % (pp<0.0001) associated with death	

Author, year	Study type	Risk of Bias	Population Description	Diagnostic Test (Index Test) Comparator (or Reference Test)	Results	GRADE Certainty Rating
					on univariable but not multivariable Cox model; on multivariable Cox, honeycombing score at baseline only independent risk factor of mortality (HR 1.23, 95% CI 1.10-1.44). Note: Unclear which variables were in multivariable Cox model (not listed/described).	

BAL: bronchoalveolar lavage; CI: confidence interval; CYC: cyclophosphamide; DLCO: Diffusing Capacity for Carbon Monoxide; FVC: Forced Vital Capacity; GGO: ground glass opacities; HR: hazard ratio; HRCT: High Resolution Computed Tomography; PAH: pulmonary arterial hypertension; PFT: Pulmonary Function Test; SSc: Systemic Sclerosis; TLC: Total Lung Capacity

Table 19-2. PICO 19 Excluded Studies

Reference	Reason for Exclusion
Goldin et al., 2008[3]	No outcome of interest
Strange et al., 2008[4]	No intervention of interest
Behr et al., 1996[5]	No comparator of interest
Padley et al., 1991[6]	Population not of interest
Silver et al., 1990[7]	No intervention of interest

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3. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367.
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PICO 20: In rheumatic disease patients with ILD, what is the impact of PFTs compared to 6-minute walk test distance on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question

Table 20-1. PICO 20 Excluded Studies

Reference	Reason for Exclusion
Solomon et al., 2022[18]	Does not address PICO
Chen et al., 2022[17]	Does not address PICO
Raghu et al., 2022[11]	Wrong study design
Nawata et al., 2021[7]	No comparator of interest
Hoa et al., 2020[1]	Does not address PICO
Narvaez et al., 2020 [19]	Does not address PICO
Volkmann et al., 2019[24]	Does not address PICO
Occhipinti et al., 2019[15]	Does not address PICO
Kafaja et al., 2018[21]	Does not address PICO
Higo et al., 2017[8]	No comparator of interest
Okamaoto et al., 2016[22]	Does not address PICO
Tashkin et al., 2016[20]	Does not address PICO
Kloth et al., 2016[16]	Does not address PICO
Moore et al., 2015[14]	Does not address PICO
Rojas-Serrano et al., 2015[13]	No comparator of interest
Mira-Avendano et al., 2013[23]	Does not address PICO
De Santis et al., 2012[4]	Does not address PICO
Volpinari et al., 2011[6]	Does not address PICO
Colaci et al., 2010[2]	Does not address PICO
Tillie-Leblond et al., 2008[12]	No comparator of interest

Reference	Reason for Exclusion
Goldin et al., 2008[10]	No comparator of interest
Strange et al., 2008[3]	Does not address PICO
Bodolay et al., 2005[9]	No comparator of interest
Behr et al., 1996[5]	Does not address PICO

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10. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367.
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19. Narvaez J, Robles-Perez A, Molina-Molina M, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. *Seminars in arthritis and rheumatism*. 2020;50(5):902-910.
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21. Kafaja S, Clements PJ, Wilhalme H, et al. Reliability and minimal clinically important differences of FVC results from the scleroderma lung studies (SLS-I and SLS-II). *American Journal of Respiratory and Critical Care Medicine*. 2018;197(5):644-652.
22. Okamoto M, Fujimoto K, Sadohara J, et al. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. *Respiratory Investigation*. 2016;54(6):445-453.
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PICO 21: In rheumatic disease patients with ILD, what is the impact of PFTs and 6-minute walk test distance compared to PFTs alone on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table . PICO 21: Excluded Studies

Reference	Reason for exclusion
Solomon et al., 2022[4]	No intervention of interest
Wu et al., 2022[2]	No intervention of interest
Narvaez et al., 2020[5]	No intervention of interest
Kafaja et al., 2018[6]	No intervention of interest
Moore et al., 2015[3]	No intervention of interest
Strange et al., 2008[1]	No intervention of interest

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PICO 22: In rheumatic disease patients with ILD, what is the impact of PFTs compared to ambulatory desaturation on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 22-1. PICO 22: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[8]	No comparator of interest
Yamaguchi et al., 2022[14]	No comparator of interest
Chen et al., 2022[15]	No comparator of interest
Solomon et al., 2022[16]	No comparator of interest
Nawata et al., 2020[6]	No comparator of interest
Narvaez et al., 2020[17]	No comparator of interest
Occhipinti et al., 2019[12]	No comparator of interest
Volkmann et al., 2019[23]	No comparator of interest
Kafaja et al., 2018[19]	No comparator of interest
Rojas-Serrano et al., 2017[22]	No comparator of interest
Kloth et al., 2016[13]	No comparator of interest
Tashkin et al., 2016[18]	No comparator of interest
Okamoto et al., 2016[20]	No comparator of interest
Rojas-Serrano et al., 2015[10]	No comparator of interest
Moore et al., 2015[11]	No comparator of interest
Mira-Avendano et al., 2013[21]	No comparator of interest
Volpinari et al., 2011[5]	No comparator of interest
Colaci et al., 2010[1]	No comparator of interest
DeSantis et al., 2010[3]	No comparator of interest
Strange et al., 2008[2]	No comparator of interest

Reference	Reason for exclusion
Tillie-Leblond et al., 2007[9]	No comparator of interest
Bodolay et al., 2005[7]	No comparator of interest
Behr et al., 1996[4]	No comparator of interest

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PICO 23: In rheumatic disease patients with ILD, what is the impact of PFTs, and high-resolution CT thorax compared to PFTs alone on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events, and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Indirect findings from 16 observational studies suggest that combining pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT) may be more helpful in monitoring ILD progression compared to any test used alone.
- Indirect evidence from 1 observational study suggests that staging of ILD as limited disease (HRCT at <20% and FVC at ≥70%) or extensive disease (HRCT at >30% and FVC at <70%) was more predictive of mortality than either HRCT (at a threshold of 20%) or FVC (at a threshold of 70%) in isolation.
- No studies addressed the impact of HRCT compared to or in addition to PFTs on treatment-related serious adverse events or testing-related adverse events.

Summary of Evidence:

We included five posthoc analyses of data from the Scleroderma Lung Study I and II (Kim H. et al., 2020,[1] Tashkin D. et al., 2016,[2] Kim H. et al., 2011,[3] Khanna D., 2011,[4] Goldin et al., 2008[5]), and 12 additional observational studies. See Table 23-1 for results of all included studies. Below, we highlight the findings from studies that include patients representing different underlying rheumatic disorders. *See Table 23-3 for additional resources to consider.*

Example of Results from Observational Studies:

Overall, the general findings of observational studies included as indirect evidence for this PICO indicate a correlation between pulmonary function tests, HRCT imaging (sometimes via quantitative imaging scores), and ILD progression among patients with rheumatic diseases. Evidence of this correlation may suggest that HRCT used in combination with pulmonary function tests is more helpful than PFTs alone in monitoring ILD progression or treatment response.

- Lee J et al., 2021[6] found that higher quantitative ILD scores based on high-resolution computed tomography were associated with lower pulmonary function among patients with rheumatoid arthritis related ILD.

- Baseline pulmonary function represented by DLCO% had a significant negative correlation with the quantitative ILD score of the whole lung ($\rho = -0.433$, $p = 0.027$)
- DLCO% also showed a positive correlation with total lung capacity (TLC) measured by HRCT using the quantitative system ($\rho = 0.377$, $p = 0.058$).

- Roca, F.et al., 2017[7] evaluated the progression of ILD among 263 patients with primary Sjogren's syndrome (21 of those with ILD). Progression was monitored through pulmonary function tests (vital capacity (VC), forced VC (FVC), and diffusing capacity for carbon monoxide (DLCO, symptoms (dyspnea), and HRCT. Overall, 7 patients with ILD deteriorated, and 12 stabilized/improved. Among those who deteriorated, DLCO was significantly lower at the last PFT assessment. No difference in symptoms (cough/dyspnea), HRCT appearance, or other presenting PFTs.
- Khanna et al., 2011[4] conducted a post-hoc analysis of the SLS-I study that evaluated the decline in ILD among 79 patients with SSc-ILD assigned to placebo (Khanna D. et al., 2011[4]). The mean decline in the unadjusted FVC % predicted during the 1-year period was 4.2 ±12.8%. At baseline, 28.5%, 43.0%, and 28.5% of patients were in the groups with disease durations of 0–2 years, 2–4 years, and >4 years, respectively. The rate of decline in the FVC % predicted was not significantly different across the 3 disease groups (P = 0.85). When stratified by baseline fibrosis on HRCT, the rate of decline in the FVC % predicted was statistically significantly greater in the group with severe fibrosis (mean annualized decline in the FVC % predicted 7.2% versus 2.7% in the groups with no or moderate fibrosis; P = 0.008). These findings suggest that a combination of HRCT and PFTs is more helpful in monitoring these patients than PFTs alone.
- Goldin et al., 2008[5] assessed the progression of ILD with HRCT among patients with limited SSc (lcSSc, n=65) and diffuse SSc (dcSSc, n=97) and found that pure ground glass opacities (GGOs) were positively associated with FVC, FEV1, but pulmonary fibrosis on HRCT was negatively associated with FVC, DLCO, TLC and positively with FEV1/FVC ratio (Goldin, J. et al., 2008[5]). Honeycomb cysts' presence was negatively associated with DLCO and TLC. The absence of a perfect correlation between HRCT features and PFTs indirectly suggests the utility of using both as monitoring methods for disease progression.
- Goh et al., 2008[8] evaluated a staging system for ILD among patients with SSc to apply within clinical practice that integrated extent of disease on HRCT (between 10 to 30%) and FVC threshold. Staging of ILD as limited disease (HRCT at <20% and FVC at ≥70%) or extensive disease (HRCT at >30% and FVC at <70%) was more predictive of mortality than either HRCT (at a threshold of 20%) or FVC (at a threshold of 70%) in isolation.

Table 23-1. Evidence for PICO 23: PFTs and high-resolution CT thorax compared to PFTs alone

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
Post-hoc Studies of Scleroderma Lung Study I and II							
Critical outcome: Responsiveness/sensitivity of change on test							Very low[1]
Kim et al., 2020[1] Date from Scleroderma Lung Study II (SLS) Using HRCT to measure patterns of ILD in response to immunosuppressive therapy of systemic sclerosis-related ILD (SSc-ILD)	Post-hoc of randomized controlled trial	High, selection bias, measurement variation, no validation by histopathology	Mean duration between baseline and follow-up CT scan was 24.6 (+/-1.9) months	97 patients with symptomatic SSc-ILD; 47 received CYC and 50 received MMF Age: 52 years % Female: 72% mean FVC at baseline: 66.3%, mean DLCO at baseline: 55%	Evaluated various changes in CT from baseline to follow-up in each of the treatment arms and between stable, improved, and worsened groups.	● During treatment, there was no significant change in transitional probabilities of ILD patterns between two treatment arms based on HRCT. ● There was mean net improvement in transitions from both lung fibrosis and ground glass to a normal pattern in both treatment arms, but essentially no significant net improvement in transitions from lung fibrosis to ground glass. ● Less baseline dyspnea was	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						associated with improvement in ground glass to normal pattern. ● Better FVC and worse skin score were associated with favorable transitions from lung fibrosis patterns to normal lung. ● Findings inconclusive if HRCT is sufficient for monitoring treatment efficacy.	
Tashkin et al., 2016[2] Date from Scleroderma Lung Study I and II (SLS I-II) To evaluate correlations between quantitative analyses of extent of lung fibrosis (QLF) or total ILD (QILD) and	Post-hoc of randomized controlled trial	High, selection bias, measurement variation, no validation by histopathology	12 months	SLS-I patients (n=158) then validation cohort from SLS-II (n=142) Mean age range: 48 years (SLS-I); 52 years (SLS-II) % Female 72%	Correlation between Lung fibrosis (QLFib) or total ILD (QILD) scores based on HRCT image analysis and pulmonary function tests (PFTs) measured at baseline Correlations were determined through regression models.	DLCO was the best variable predicting HRCT measured QLFib-whole lung and QILD-zones FEV1/FVC had a lower, but significant correlation with HRCT QLFib-whole lung and QILD-zones FVC had the lowest correlation with HRCT QLFib-whole lung and QILD-zones	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
traditional physiological and patient-centred indices of disease in patients with active SSc-ILD from two large, randomised, interventional studies (Scleroderma Lung Study I and II, or SLS I and II).						PFTs alone may not be the best measure of lung disease among patients with systemic sclerosis and ILD.	
Kim et al., 2011[3] Date from Scleroderma Lung Study I (SLS) Purpose: to determine if quantitative lung fibrosis scores obtained through HRCT can provide a quantitative tool for assessing treatment efficacy.	Post-hoc of randomized controlled trial	High, selection bias, potential measurement error	12 months	98 patients with systemic sclerosis (SSc-ILD) from SLS I study who had digital HRCT images at baseline and 12 months. 41 patients got cyclophosphamide and 42 got placebo	Images from high-resolution computed tomography (HRCT) were quantified into quantitative lung fibrosis (QLF) scores using changes in texture that quantify lung fibrosis Comparisons were made to pulmonary function tests (PFTs) and dyspnea score to establish associations.	Findings based on the most severe zone (covering the chest into upper, middle, and lower zones) identified at baseline and the whole chest. **12 months follow-up** QLF scores decreased by 2.6% in the cyclophosphamide group, whereas they increased by 9.1% in the placebo group, leading to ~12% difference (p=0.0027). Between-treatment difference in whole lung QLF was ~5% (p=0.0190) Significant associations were observed between	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						changes in QLF and FVC (r=−0.33), dyspnea score (r=−0.29), and consensus visual score of lung fibrosis (p=0.001). The correlation coefficients were far away from 0 suggesting a combination of measures and evaluations are more helpful for monitoring.	
Khanna et al., 2011[4] Date from Scleroderma Lung Study I (SLS-I) Purpose: to determine if quantitative lung fibrosis scores obtained through HRCT can provide a quantitative tool for assessing treatment efficacy.	Post-hoc of randomized controlled trial	High, selection bias, potential measurement error	12 months period of evaluation	Subset of 79 patients with systemic sclerosis (SSc)-ILD who were assigned placebo in SLS-I Age: 48.3 years % Female: 62%	Patients divided into 3 groups based on duration of SSc. Analyzing rate of decline in %FVC over 1 year period based on duration of disease and based on fibrosis severity by HRCT.	**Disease duration, years** 0–2 years: n= 17; FVC decline at 12 mos: 4.4 ± 18.8, p= 0.85 2–4 years: n=29, FVC decline at 12 mos: 4.4 ±10.1 >4 years: n=18, FVC decline at 12 mos: 3.5 ± 10.1 **HRCT fibrosis score** 0–2: n=40, FVC decline: 2.7 ±12.8, p= 0.008 3–4: n= 25, FVC decline: 7.2 ±11.8	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						HRCT ground-glass opacification score 0–1: n=55, FVC decline 4.9 ± 13.0, p= 0.61 2–3: n=10, FVC decline: 1.8 ± 9.8 **HRCT honeycombing score** 0: n=38, FVC decline 3.8 ± 14.5, p= 0.96 ≥1: n=27, FVC decline 5.3 ±9.2 **Overall:** n= 66, FVC decline 4.2 ±12.8 The mean SD decline in the unadjusted FVC % predicted during the 1-year period was 4.2 ±12.8%. At baseline, 28.5%, 43.0%, and 28.5% of patients were in the groups with disease durations of 0–2 years, 2–4 years, and >4 years, respectively. The rate of decline in the FVC % predicted was not significantly different across the 3 disease groups (P = 0.85). When stratified by baseline fibrosis on HRCT, the rate of	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						decline in the FVC % predicted was statistically significantly greater in the group with severe fibrosis (mean annualized decline in the FVC % predicted 7.2% versus 2.7% in the groups with no or moderate fibrosis; P = 0.008).	
Goldin et al., 2008[5] Date from Scleroderma Lung Study I (SLS-I) Purpose: to determine if quantitative lung fibrosis scores obtained through HRCT can provide a quantitative tool for assessing treatment efficacy.	Post-hoc of SLS-I Seeks to investigate the frequency, characteristics, and likelihood of progression of ILD in patients with diffuse versus patients with limited SSc.	High, selection bias, potential measurement error	12 months	N=162 patients with SSc N=65 limited (lc)SSc (40%) and n=97 diffuse (dc)SSc (60%). A total of n=79 randomized to the placebo control group. % Female: 70%) Age: 51 +/- 12.3 Of n=162 subjects, n=148 (91.4%) underwent BAL and HRCT.	Pulmonary function tests (PFTs) were performed within 4 weeks of the enrollment HRCT was performed within 4 weeks of BAL. Results focused on correlation between HRCT findings, PFTs, BAL evidence for alveolitis.	Patients were considered to have active ILD based on the presence of alveolitis on bronchoalveolar lavage (BAL) or HRCT, or any ground-glass opacities (GGO), Grade 2 exertional dyspnea on the Mahler Dyspnea Index, and baseline FVC between 45-80% predicted. Patients with severely reduced PFTs were excluded. Pure GGOs were positively associated with FVC and FEV1. Pulmonary fibrosis was negatively	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						associated with FVC, DLCO, TLC and positively with FEV1/FVC ratio. Honeycomb cysts presence was negatively associated with DLCO and TLC. The absence of a perfect correlation between HRCT features and PFTs may indirectly suggest utility to both monitoring methods.	
Findings of Other Observational Studies							
Critical outcome: Responsiveness/sensitivity of change on test							Very low[1]
Shao, et al. 2022[14]	Retrospective cohort	High, retrospective extraction of data, small study, potential selection bias	1 year	142 patients with fibrotic ILD included in analysis (of 209 patients enrolled between 2017 and 2021). Age: 67 years % Female: 36.6% Connective tissue disease associated ILD: n=34 (24%) Rheumatoid arthritis: n=10 Systemic sclerosis: n=10	Purpose: To develop a scoring system for estimating 1-year progression-risk in a cohort of patient with radiologically evident fibrotic ILD. Two-thirds of patients were randomly a derivation cohort which examined the impact of age, sex, baseline lung function, CT finding scores, and blood	Significant traction bronchiectasis (score 5-6 versus 0), but not FVC or DLOC were significantly associated with progression at 1-year in univariate and multivariable analysis, underscoring utility of HRCT over PFTs for evaluating the likelihood of progression. Honeycombing, traction	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
				Antisynthetase syndrome: myositis: n=3 ANCA-associated vasculitis: n=2 Systemic lupus: n=2 Sjogren syndrome: n=2 Other: 3 Idiopathic NSIP: n=30 (21%) IPAF: n=18 (13%) IPF: n=23 (16%) Other ILD: n=6 (4%)	biomarkers on 1-year disease progression. Critical outcome: progression at 1 year. This was a composite endpoint of either ≥10% relative decrease in FVC, ≥15% in DLCO, by death or lung transplant within the first year after primary evaluation and ILD-board discussion, regardless of when the event had occurred within that time span.	bronchiectasis, and blood monocyte count were included in the score which predicted progression (progression was assessed by PFTs and vital status). These highlight need for HRCT in addition to PFTs to assess and predict disease related outcomes.	
Tardella et al., 2022[9]	Retrospective cohort study	High, small study, selection bias due largely to non-randomized, retrospective nature of study	18 months of therapy	75 patients with RA-ILD receiving abatacept (ABA, 31 patients) or Janus-kinase (JAK) inhibitors (44 patients)	HRCT, FVC and DLCO, Borg's dyspnea index.	In ABA group, 11% patients showed HRCT deterioration, 73% were stable, 16% improved on HRCT. In JAK group, 16% deteriorated, 64% were stable, 19% improved on HRCT. Borg dyspnea index was significantly different from baseline to 18 months in both groups DLCO, FVC, HRCT-CaM fibrosis changes were not significantly different from	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						baseline to 18 months in both groups. HRCT helpful in addition to PFTs. Unclear if helpful in addition to history/physical. Borg Dyspnea Index: ABA: Time 0 (T0): 2.54±1.23; (T18) 1.90±1.01, p<0.01 JAK: T0: 0.01 2.51±1.22; T18 1.87±1.11, p= 0.03 DLco (% predicted) ABA T0: 58.69±8.24; T18: 61.26±11.23, p= 0.22 JAK T0: 59.72±8.56; T18: 62.75±11.84, p=0.28 FVC (% predicted) ABA T0: 82.29±4.86; T18: 81.24±11.97, p=0.59 JAK: T0: 81.18±5.07; T18: 79.59±14.02, p= 0.55 HRCT-CaM fibrosis (%) ABA T0: 19.41±5.89; T18: 18.94±6.06, p= 0.71	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						JAK: T0:18.54±6.31, T18: 17.52±6.35, p= 0.53	
Lee et al., 2021[6]	Retrospective study for cohort 1 (n=26), prospective study for cohort 2 (n=34) Correlated the HRCT imaging analyses with the results of PFT, serum biomarker, and visual assessment by an expert radiologist.	High; selection bias, did not control for all confounders.	Interval of 1.5 years (+/-1.0)	2 cohorts of patients with rheumatoid arthritis related ILD (cohort 1, n= 26 patients, cohort 2, n= 34 patients) Mean age: 65 years % Female: 67%	High-resolution computed tomography with matched pulmonary function tests Focus was on association between quantitative ILD score obtained through HRCT and pulmonary function.	Association Patterns between QILD Score and Pulmonary Function Higher QILD score was associated with lower pulmonary function ● Baseline pulmonary function represented by DLCO% had significant negative correlation with quantitative ILD score of the whole lung ($\rho = -0.433$, $p = 0.027$) ● DLCO% also showed positive correlation with total lung capacity (TLC) measured by HRCT using the quantitative	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						system (ρ= 0.377, p = 0.058). ● Pulmonary function represented by FVC% was weakly negatively correlated with quantitative ILD score of the whole lung (ρ = −0.298, p = 0.140) and had significant positive correlation with TLC (ρ = 0.637, p < 0.001)	
Wada et al., 2020[10]	Retrospective cohort study	High, small study, potential selection bias (due to attrition), measurement bias	Baseline, 6-, 12-, and 18-months post-transplant	53 patients with scleroderma who underwent autologous hematopoietic stem cell transplant (AHSCT) 20 patients excluded due to lack of follow-up data. Mean age: 35 years % Female: 75%	All patients underwent HRCT imaging and PFTs at baseline and at 6, 12, and 18 months after AHSCT. 18 months after AHSCT, patients were divided into 2 groups by pulmonary response. Best response = increase in %FVC at least 10%, stable response = FVC change less than 10%.	**Best response group n=15):** Significant increase in FVC, TLC, mean lung density. **Stable disease group (n-18):** No change in FVC from baseline to 18 months post but significant increase in TLC (p=0.05), no significant change in mean lung density.	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						Pulmonary HRCT densities showed moderate correlations with pulmonary function.	
Occhipinti et al., 2019[11]	Retrospective cohort study Evaluated quantitative analysis (QA) of CT chest compared with other parameters	High, did not seem to control for length of follow-up, small sample size, unclear treatment effect.	Mean follow-up of 26 +/- 13 months, assessed changes from baseline to last visit.	31 patients with scleroderma ILD Mean age: 51 years % Female: 77%	Semi QA score, QA score of CT scans, compared to PFT parameters and vascular analysis and total lung volume. Assessed outcome after 26+/-13 months	Negative correlation between PFT and semi-QA and QA scores, correlation was stronger in the latter. Strongest correlation between % ground glass and % ground glass + % reticulations and with %TLC and %FVC. Variations in QA patterns between baseline and follow-up were not accurate (AUC:0.50 to 0.70; p>0.05) in predicting disease progression as assessed by PFT. Therefore, need HRCT in addition to PFTs for optimal monitoring/evaluation.	
Roca et al., 2017[7]	Retrospective cohort study	High, very small study (small number of patients with ILD),	Initial assessment and median follow-up	263 patients with primary Sjogren's syndrome, 21 of those with ILD.	PFT: vital capacity (VC), forced VC (FVC), and diffusing capacity for carbon monoxide (DLCO).	7 patients with ILD deteriorated, 12 stabilized/improved. Among those who deteriorated, DLCO	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
		significant heterogeneity in HRCT scans.	of ILD patients was 24 months	ILD patients consisted of 3 men and 21 women.	HRCT scan was performed to evaluate abnormalities consistent with ILD, i.e.: parenchymal micronodules/nodules, irregular linear opacities, irregularity of the interfaces between peripheral pleura and aerated lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectasis or bronchiectasis]. HRCT pattern has been correlated with pulmonary histological findings, i.e.: 1) cryptogenic organizing pneumonia (COP) is mainly characterized by consolidation and linear opacities; 2) nonspecific interstitial pneumonia (NSIP) is principally defined by ground-glass opacities and irregular linear opacities; 3) usual interstitial pneumonia (UIP) is mainly characterized by honeycombing and traction bronchiectasis; and 4) lymphoid	was significantly lower at last PFT assessment. No difference in symptoms (cough/dyspnea), HRCT appearance, or presenting PFTs. **Pulmonary characteristics** ● Cough: Deteriorated: 5 (71.4%); Improved: 7 (58.3%), p= 0.67 ● Dyspnea: Deteriorated: 6 (85.7%); Improved: 6 (50%), p= 0.17 **HRCT scan pattern** ● NSIP: Deteriorated: 3 (42.9%); Improved: 4 (33.3%) ● UIP: Deteriorated: 3 (42.9%); Improved: 2 (16.7%) ● COP: Deteriorated: 0	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
					interstitial pneumonia (LIP) is principally defined by centrolobular and subpleural nodes, cysts and ground-glass opacities.	(0%); Improved: 2 (16.7%) ● LIP: Deteriorated: 0 (0%); Improved: 2 (16.7%) /Undetermined: Deteriorated: 1 (14.3%); Improved: 2 (16.7%) **PFTs at last follow-up** ● VC (%): Deteriorated: 85%, range: 44–126; Improved 113%, range: 83–154, p= 0.15 ● FVC (%): Deteriorated: 78%, range: 45–135; Improved: 116%, range: 85–150, p= 0.11 ● DLCO (%): Deteriorated: 47%, range: 14-65; 64%, range:54–88, p= 0.048 **Mortality**	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						• Deteriorated: 1% (14.3); Improved: 1% (8.3), p=1.0	
Moore et al., 2013[12] To evaluate the relationship between serial HRCTs, pulmonary function tests (PFTs) and outcome in SSc-ILD; and to quantify change in HRCT grade over time and correlate this with change in PFTs.	Retrospective cohort	High, retrospective, unknown confounders for PFTs	Mean follow-up time of 3.5 (+/-2.9) years	172 patients with systemic sclerosis (SSc)-ILD patients	Serial HRCT and serial PFTs Primary outcome: Composite outcome of deterioration (need for O2, death [all cause], lung transplant)	Baseline HRCT grade was independently predictive of outcome, with an adjusted hazard ratio (adj. HR) = 3.0, 95% CI 1.2, 7.5 and P = 0.02. In time-varying covariate models (based on 1309 serial PFTs and 353 serial HRCTs in 172 patients), serial diffusing capacity of the lung for carbon monoxide by alveolar volume ratio (ml/min/mmHg/l) (aHR = 0.4; 95% CI 0.3, 0.7; P = 0.001) and forced vital capacity (dl) (aHR = 0.9; 95% CI 0.8, 0.97; P = 0.008), were also strongly predictive of outcome. Authors concluded that grading % of SSc-ILD on HRCT, utilizing FVC where uncertain, is simple and quick.	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
Tanizawa et al., 2013[13]	Retrospective cohort	High, small cohort and multiple possible confounders; retrospective	Median follow-up of 714 days from diagnosis	51 patients with Myositis-ILD	Clinical symptoms, serologic measures, HRCT, PFT parameters Primary outcome: 90-day mortality and overall survival	FVC/DLCO were not associated with survival or 90-day mortality. Among HRCT features, only lower consolidation/ground glass attenuation pattern were significantly associated with survival/90-day mortality. HRCT is more helpful than PFTs alone.	
Critical outcome: Mortality							Very low[2]
Waseda et al., 2022[15]	Retrospective cohort	High, retrospective, missing data, low inter-observer agreement.	90 day and 1 year survival	20 patients with MDA-5 positive DM. Of them, 14 had ADM, 19 had rapid onset disease. 7 men and 13 women Mean age: 53.6 ± 13.5 years; range 24–75 years. 13 never smokers, 6 ex-smokers, 1 unknown.	Purpose: (1) investigate the detailed lung CT characteristics of patients with anti-MDA5-ILD, aided by radiologists, and (2) determine whether the overall high-resolution CT (HRCT) score can be used to predict the outcomes of patients with anti-MDA5-ILD. Evaluated baseline features associated with 90-day and 1-year survival.	Bilateral ground-glass attenuation, air-space consolidation, and reticular shadows were observed in 20 (100%), 15 (75%), and 3 (15%) patients, respectively. The spread of air-space consolidation was 6.0 ± 5.6% (mean ± standard deviation). Univariate analysis revealed that high Krebs von den Lungen-6, high	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
					Performed comparison between the death and survival groups using Cox regression analysis. Also, the overall survival rates after 90 days and 1 year were calculated using the Kaplan–Meier method.	spread of consolidation, low partial pressure of oxygen, and low %FVC were significant predictors for poor survival. The final radiological diagnoses were nonspecific interstitial pneumonia and organizing pneumonia (OP) in 2 (10%) and 16 (80%) patients, respectively. Further, 30% of OP patients showed fibrosis. This suggests that both PFTs and HRCT are helpful for predicting outcomes The overall survival rates at 90 days and 1 year were 80.0% and 64.6%, respectively, and there were no further deaths after 1 year.	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
Goh et al., 2008[8]	Prospective cohort study	High, test readers not blinded, limited confounders considered	120 months of follow-up	215 patients with SSc and ILD, none of them had overlapping features. 19 patients had pulmonary hypertension 28% (n=61) patients were getting treatment at presentation, another 18% (n=38) patients started treatment within 3 months of presentation. Age: 49.1 years Male/female ratio: 41/174	Compared staging algorithm using combination of HRCT and pulmonary function test to HRCT and pulmonary function alone. The algorithm classified the extent of ILD on HRCT (measured between 10% minimal disease and >30% severe disease) and FVC threshold as limited or extensive. Limited disease was classified as extent on HRCT <10% and FVC threshold ≥70% and extensive disease as HRCT >30%); and FVC threshold of <70%. Critical outcome: mortality	**Primary results:** This algorithm system (hazards ratio [HR], 3.46; 95% confidence interval [CI], 2.19–5.46; P=0.0005) was more discriminatory than an HRCT threshold of 20% (HR, 2.48; 95% CI, 1.57–3.92; P=0.0005) or an FVC threshold of 70% (HR, 2.11; 95% CI, 1.34–3.32; P=0.001). **Other results:** Univariate analysis: • Mortality was strongly linked to baseline DLCO, extent of disease on HRCT, extent of reticular pattern on HRCT, presence of pulmonary hypertension. • Baseline PFTs, extent of disease on HRCT, extent	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						of reticular pattern on HRCT linked to decline in FVC, decline in DLCO, and progression-free survival • Extent of reticular pattern was the strongest determinant of time to decline in FVC and progression free survival Multivariate analysis: • HRCT disease extent, DLCO, PH presence were equally predictive of mortality • HRCT disease extent was more predictive of mortality than the extent of reticular pattern The staging system was the strongest determinant of mortality (HR, 3.66; 95% CI, 2.25–5.97; P, 0.0005) when age, sex, smoking status,	

Author, year	Study Design	Risk of bias	Follow-up	Population Description	Treatment/comparator	Results	GRADE rating
						and the presence of PH were considered. Staging of ILD as limited or extensive had a greater prognostic value than either FVC or HRTC in isolation. Therefore, obtaining the combination of both for patient monitoring is best.	

[1]Certainty of evidence for responsiveness of test downgraded to very low due to serious risk of bias, indirectness, and imprecision
[2]Certainy of evidence for mortality downgraded to very low dues to serious risk of bias, indirectness, and imprecision (single study measuring this outcome)

SLS: Scleroderma Lung Study II **, SSc:ILD**: systemic sclerosis: related ILD, **HRCT**: high-resolution computed tomography, **PFT**: pulmonary function test, **QLFib**: Quantitative Lung fibrosis, **QILD**: total ILD scores, **FEV1**: Forced expiry volume, **QLF**: quantitative lung fibrosis, **BAL**: bronchoalveolar lavage, **GGO**: ground glass opacities, **TLC**: total lung capacity, **JAK**: Janus kinase, **AHSCT**: autologous hematopoietic stem cell transplant**, QA**: quantitative analysis, **AUC**: Area under the curve, **FVC**: Forced vital, **DLCO**: diffusing capacity for carbon monoxide, **COP**: cryptogenic organizing pneumonia, **NSIP**: nonspecific interstitial pneumonia, **UIP**: usual interstitial pneumonia, **LIP**: lymphoid interstitial pneumonia

Table 23-2. PICO 23: Excluded Studies

Reference	Reason for Exclusion
Chen et al., 2022[16]	Does not address PICO
Denton et al. 2022[17]	Does not address PICO
Raghu et al., 2022[18]	Not a study design of interest
Solomon et al., 2022[19]	No outcome of interest
Wu et al., 2022[20]	No comparator of interest
Chassagon et al., 2021[21]	Does not address PICO
Cronin et al., 2021[22]	No comparator of interest
Tyker et al., 2021[23]	No comparator of interest
Xu et al., 2021[24]	Does not address PICO
Yang et al., 2021[25]	Does not address PICO
Narvaez et al., 2020[26]	No comparator of interest
Xu et al., 2020[27]	Does not address PICO
Fu et al., 2019[28]	Does not address PICO
Kafaja et al., 2018[29]	No outcome of interest
Ariani et al., 2017[30]	No comparator of interest
Rojas-Serrano J, et al., 2017[31]	Does not address PICO
Sanges et al., 2017[32]	No comparator or outcome of interest.
Kloth et al., 2016[33]	Does not address PICO
Kim et al., 2016[34]	No comparator of interest
Okamoto et al., 2016[35]	Does not address PICO
Ikeda et al., 2015[36]	No outcomes of interest
Moore et al., 2015[37]	No comparator of interest
Rojas-Serrano et al., 2015[38]	Does not address PICO
Zou et al., 2015[39]	Does not address PICO
Mira-Avendano et al., 2013[40]	No comparator of interest
Tanizawa et al., 2011[41]	No comparator of interest
Volpinari et al., 2011[42]	No comparator of interest
Colaci et al., 2010[43]	Does not address PICO

Reference	Reason for Exclusion
DeSantis et al., 2010[44]	Does not address PICO
Kim et al., 2010[45]	Does not address PICO
Marten et al., 2009[46]	Does not address PICO
Strange et al., 2008[47]	Does not address PICO
Tillie-Leblond et al., 2008[48]	Does not address PICO
Camiciottoli et al., 2007[49]	No outcomes of interest
Bodolay et al., 2005[50]	No comparator of interest
Schnabel et al., 2003[51]	No comparator of interest
Behr et al., 1996[52]	No comparator of interest

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Table 23-3: Additional Resources to Consider

Reference	Note
Carnevale A, Silva M, Maietti E, Milanese G, Saracco M, Parisi S, et al. Longitudinal change during follow-up of systemic sclerosis: correlation between high-resolution computed tomography and pulmonary function tests. Clin Rheumatol. 2021;40:213–9.	In SSc patients, chest HRCT performed every 12-24 months can detect minimal but significant changes in ILD extent, even in subjects with stable pulmonary function. PFT changes in 12-24 months are related to the radiological ILD progression. Repeated chest HRCT may be useful for monitoring SSc-ILD when performed within 12 to 24 months from baseline to promptly detect progression and possibly impact on prognosis

PICO 24: In rheumatic disease patients with ILD, what is the impact of 6-minute walk test distance compared to ambulatory desaturation on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 24-1. PICO 24: Excluded Studies

Reference	Reason for exclusion
Yamaguchi et al., 2022[2]	No intervention of interest
Sanges et al., 2017[1]	No outcomes of interest

References

1. Sanges S, Giovannelli J, Sobanski V, et al. Factors associated with the 6-minute walk distance in patients with systemic sclerosis. *Arthritis research & therapy*. 2017;19(1):279.
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PICO 25: In rheumatic disease patients with ILD, what is the impact of mycophenolate compared to no mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, found that treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Summary: Four studies (2 RCTs, 2 observational studies) address this PICO question.[1-4]

Regarding treatment-associated disease-related outcomes:

Naidu et al., 2020[1] conducted a double-blind randomized placebo-controlled trial of MMF (2g BID) vs. placebo among 41 patients with SSc-ILD. 15 MMF-treated patients and 19 placebo-treated patients completed the study. Treatment failure requiring withdrawal from the study protocol was defined as worsening at 3 months after randomization. Regarding the primary outcome (median change from baseline FVC at 6 months), the FVC decreased by a median of 2.7% (range − 21 to 9; p = 0.307) in the MMF group and increased by a median of 1% (range − 6 to 10; p = 0.222) in the placebo group. The mean absolute difference in FVC change from baseline to 6 months between MMF and placebo groups was 3.1% [95% confidence interval (CI), − 1.0 to 7.3%; p = 0.131]. There was no significant difference in the change in FVC from baseline to 3 and 6 months between both the groups (p = 0.339) on a multiple repeated-measures ANOVA analysis. Based on the change in FVC, subjects were also categorized as: improved/stabilized (any increase or less than 10 absolute points fall in percent-predicted FVC at baseline) and worsened (more than or equal to 10 absolute

points fall in percent-predicted FVC at baseline). 15 (75%) subjects in the MMF arm had improvement or stabilization of FVC at 6 months compared to 19 (90.5%) subjects in the placebo arm. None of the subjects in either group had an improvement of FVC more than 10% absolute points from baseline (see Table 25-1). There was no significant difference in the median change in SF-36 PCS and MCS scores between the two groups after adjusting for baseline values. The median (range) change in SF-36 Physical component score was 7 (-1.2, 14.30) and 5 (-7.5, 20.8) in MMF and placebo arms, respectively. The median change in SF-36 Mental component score was 8.3 (-3.8, 18.4) and 6 (-10, 30.7) in MMF and placebo arms, respectively. The minimally important difference to consider improvement in the transitional dyspnea index focal score is + 1 or more. This difference was seen in 10 (66.7%) subjects in the MMF group and 10 (52.6%) subjects in the placebo group (see Table 25-1). Among subjects with anti-topoisomerase antibody positivity, the mean absolute difference in percent-predicted FVC at 6 months between MMF and placebo groups was 3.7% (95% CI − 1.9% to 9.4%, p = 0.184), indicating no significant difference between the two groups. Overall, regarding disease-related outcomes, in this pilot study, MMF did not result in significant improvement in lung function in SSc-ILD compared to no MMF (placebo). Weaknesses include that the endpoint of 6 months was shorter than typical SSc-ILD trials and that the maximum dose of MMF (3g/day) was not used.

Adler et al., 2018[2] retrospectively studied 3778 patients with SSc-ILD in the EUSTAR cohort over a follow-up ranging from 1 month to 13 years. Those patients who were on MMF had severe baseline impairment of FVC and DLCO. Regarding DLCO trend, there was a negative multiplicative effect of MMF, meaning an even steeper decrease in the rate of decline of DLCO than the general trend. Conversely, there was a positive multiplicative effect in patients in the never-immunosuppressed group indicating a less steep decline in DLCO. This is an observational study with a high risk of confounding by indication. See Table 25-2 for additional details.
Volkmann et al., 2017[3] used data from SLS-I and SLS-II to compare MMF (from SLS-II) and placebo (from SLS-I) that included 69 MMF-treated patients (up to 3g/day as tolerated) and 79 placebo-treated patients. These arms are from two different studies that had similar inclusion criteria. The primary outcome was a change in FVC% predicted in a linear mixed-effects model. Secondary outcomes were modeled changes in DLCO, TDI, and safety (see Table 25-2). After controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF was associated with improved % predicted FVC over 24 months. The test of the overall treatment group effect for the entire model was highly significant (P = 0.0001). Using the intent-to-treat population, 64.4% and 71.7% of MMF-treated patients had any improvement in % predicted FVC at 12 and 24 months, respectively, and most patients who experienced an improvement in % predicted FVC at 24 months had an absolute improvement of >5%. After controlling for baseline % predicted DLCO and baseline whole lung QILD score, treatment with MMF was associated with improved % predicted

DLCO over 24 months (P = 0.0001). After adjustment for baseline dyspnea index, treatment with MMF was associated with improvement in dyspnea compared with placebo as measured by the TDI (P = 0.0112).

Matson et al., 2022[4], conducted an observational study of 212 patients with rheumatoid arthritis associated ILD of which 77 were treated with MMF, 92 treated with azathioprine, and 43 with rituximab. In an analysis combining all three treatment agents, choice of immunosuppressive agent did not significantly impact pulmonary function trajectory defined by FVC and DLCO change at 12-months. In the combined analysis of all three agents, there was an improvement in forced vital capacity (FVC) % predicted after 12 months of treatment compared to the potential 12-month response without treatment [+3.90%, p=< 0.001; 95% CI, (1.95, 5.84)].[4]

Regarding treatment-related adverse events:
Naidu et al., 2020[1] conducted a double-blind RCT comparing MMF and placebo as described above. There was no significant difference in the rate of adverse events (any) between the treatment and control groups. Specifically, in the MMF group, adverse events were recorded at a rate of 1.6 episodes/subject, while in the placebo group, they were recorded at 1.14 episodes/subject (p = 0.147). There was 1 serious adverse event in the MMF group vs. 0 in the placebo group. Regarding diarrhea, there were 15 episodes with MMF vs 7 episodes with placebo (no p-value shown or standard deviation). A higher proportion of subjects in the MMF arm (50%) developed diarrhea compared to the placebo (23.8%), but the difference was not statistically significant (p=0.095) (see Table 25-1). The number of infections in both groups was similar (14 with MMF versus 10 with placebo, p = 0.347).

Volkmann et al., 2017[3] used data from SLS-I and SLS-II to compare MMF (from SLS-II) and placebo (from SLS-I), as described above. Regarding serious adverse effects, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in the placebo vs. 27 in the MMF arm). There were 5 deaths with MMF and 6 deaths with placebo, which was not significantly different. Regarding any non-serious adverse event, there were 7 in the placebo arm and 23 in the MMF arm. The breakdown of those non-serious adverse events are as follows: (leukopenia (4 AEs in the MMF arm and none in the placebo arm), neutropenia (3 AEs in the MMF arm and none in the placebo arm), anemia (8 AEs in the MMF arm and 1 in the placebo arm), and pneumonia (5 AEs in the MMF arm and 1 in the placebo arm)) occurred in more MMF-treated patients in SLS II than placebo-treated patients in SLS I.

Matson et al., 2022[4], conducted an observational cohort study among patients taking azathioprine, MMF, or rituximab. Among MMF users, there were 12 of 77 experienced an adverse event (15.6%), 3 of 77 patients discontinued MMF due to treatment-related side

effects. GI upset occurred in 5 (6.5%) recurrent infection occurred in 2 (2.6%), cytopenia occurred in 2 (2.6%), no patients had elevated liver enzymes, and nonspecific symptoms were reported in 5 patients (5.4%). There were no statistical comparisons performed between groups in this descriptive analysis.[4]

Table 25-1: PICO 25: Mycophenolate vs no mycophenolate as first line ILD treatment

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse Events, Any												
1 Volkmann et al., [3]	randomized trial	not serious	not serious	not serious	very serious[a]		23/69 (33.3%)	7/79 (8.9%)	RR 3.76 (1.72 to 8.22)	245 more per 1,000 (from 64 more to 640 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Event												
2 Volkmann et al., [3]; Naidu et al., [1]	randomized trials	not serious	not serious	not serious	serious[a,b]		28/89 (31.5%)	38/100 (38.0%)	**OR 0.74** (0.39 to 1.40)	**68 fewer per 1,000** (from 187 fewer to 82 more)	⊕⊕◯◯ Low	CRITICAL
AE, diarrhea												
1 Naidu et al., [1]	randomized trial	not serious	not serious	not serious	serious[a,b]		10/20 (50.0%)	5/21 (23.8%)	RR 2.10 (0.87 to 5.07)	262 more per 1,000 (from 31 fewer to 969 more)	⊕⊕◯◯ Low	IMPORTANT
Death												
1 Volkmann et al., [3]	randomized trial	not serious	not serious	not serious	serious[a, b]		5/69 (7.2%)	6/79 (7.6%)	RR 0.95 (0.30 to 2.99)	4 fewer per 1,000 (from 53 fewer to 151 more)	⊕⊕◯◯ Low	CRITICAL
ILD improvement/stabilized proportion; per protocol analysis, 6 months												
1 Naidu et al., [1]	randomized trial	not serious	not serious	serious[c]	serious[a, b]		15/20 (75.0%)	19/21 (90.5%)	RR 0.83 (0.62 to 1.11)	154 fewer per 1,000 (from 344 fewer to 100 more)	⊕◯◯◯ Very low	IMPORTANT
TDI Score meeting minimally important difference (MID) of improvement (MID defined as TDI focal score of+1 or more)												
1 Naidu et al., [1]	randomized trial	not serious	not serious	not serious	serious[a,b,]		10/15 (66.7%)	10/19 (52.6%)	RR 1.27 (0.73 to 2.21)	142 more per 1,000 (from 142 fewer to 637 more)	⊕⊕◯◯ Low	IMPORTANT

TDI score, 12 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	not serious	serious[a,b]		69	79	-	MD 2.52 higher (1.22 higher to 3.82 higher)	⊕⊕◯◯ Low	IMPORTANT

FVC % predicted, 12 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	serious[c]	serious[a]		69	79	-	MD 5.11 higher (2.88 higher to 7.34 higher)	⊕⊕◯◯ Low	IMPORTANT

DLCO % predicted, 12 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	serious[c]	serious[a,b]		69	79	-	MD 4.29 higher (0.92 higher to 7.66 higher)	⊕⊕◯◯ Low	IMPORTANT

FVC % predicted, 12 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	serious[c]	serious[a]		69	79	-	MD 5.11 higher (2.88 higher to 7.34 higher)	⊕⊕◯◯ Low	IMPORTANT

FVC % predicted mean change, 6 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	serious[c]	serious[a]		69	79	-	MD 3.45 higher (1.58 higher to 5.32 higher)	⊕⊕◯◯ Low	IMPORTANT

FVC % predicted change, 24 months

1 Volkmann et al., 2998	randomized trial	not serious	not serious	serious[c]	serious[a]		69	79	-	MD 5.44 higher (1.94 higher to 8.94 higher)	⊕⊕◯◯ Low	IMPORTANT

DLCO % predicted, 6 months

1 Volkmann et al., [3]	randomized trial	not serious	not serious	serious[c]	serious[a,b]		69	79	-	MD 2.27 higher (0.72 lower to 5.26 higher)	⊕⊕◯◯ Low	IMPORTANT

DLCO % predicted, 24 months

1 Volkmann et al., [3]	randomized trial	not serious	not serious	serious[c]	serious[a,b]		69	79	-	MD 4.64 higher (0.93 higher to 8.35 higher)	⊕⊕◯◯ Low	IMPORTANT

AE: adverse events; MD: mean difference; RR: risk ratio

Explanations

a. Low number of patients

b. Wide confidence intervals (95% CI includes the line of no difference, suggests possibility of substantial benefit and harm)

c. Surrogate outcome for mortality

Table 25-2: PICO 25: Additional data for Mycophenolate vs no mycophenolate as first line ILD treatment

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Naidu et al., 2020[1]	Double blind RCT	Low, RCT, blinded, ITT	6 months	41 patients with SSc-ILD with moderate to severe impairment; median age 40, 39% women	Treatment: MMF up titrated to 2g BID (n=20) The median dose of MMF reached was 2 gm/day (range 1.5–2). Comparator: placebo (n=21) .	15 MMF treated patients and 19 placebo treated patients completed the study. Treatment failure requiring withdrawal from the study protocol was defined as worsening at 3 months after randomization. Median (rather than mean) change in baseline to 6-month values were reported therefore included in this table rather than RevMan. (1) Primary outcome = change from baseline FVC at 6 months. The FVC decreased by a median of 2.7% (range – 21 to 9; p = 0.307) in the MMF group and increased by a median of 1% (range – 6 to 10; p = 0.222) in the placebo group. The mean absolute difference in FVC change from baseline to 6 months between MMF and placebo groups was 3.1% [95% confidence interval (CI), − 1.0 to 7.3%; p = 0.131]. There was no significant difference in the change in FVC from baseline to 3 and 6 months between both the groups (p = 0.339) on a multiple repeated-measures ANOVA analysis (2) Based on the change in FVC, subjects were categorized as: improved/stabilized (any increase or less than 10 absolute points fall in percent- predicted FVC at baseline) and worsened (more than or equal to 10 absolute points fall in percent-predicted FVC at baseline).

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
						Secondary outcome measures: (3) Quality of Life: change from baseline in SF36v2 scores • There was no significant difference in the **median** change in PCS and MCS scores of SF36v2 and TDI between the two groups after adjusting for baseline values. • Median (range) change in SF-36 Physical component score in MMF 7 (-1.2, 14.30 and placebo 5 (-7.5, 20.8) • Median change in SF-36 Mental component score MMF group 8.3 (-3.8, 18.4) and placebo group 6 (-10, 30.7) (4) FVC in ATA-positive subjects at 6 months Among subjects with ATA positivity, the mean absolute difference in percent-predicted FVC at 6 months between MMF and placebo groups was 3.7% (95% CI – 1.9% to 9.4%, p = 0.184), indicating no significant difference between the two groups. (5) The number of serious and non-serious adverse events - In the MMF group, adverse events were recorded at a rate of 1.6 episodes/subject, while in placebo group they were recorded at 1.14 episodes/subject (p = 0.147). (6) Change in 6MWD (median (range) 0 (-113, 240) vs 0 (-180, 170) in MMF vs PBO respectively, p=0.522
Adler et al., 2018[2]	Retrospecti ve observation	High (observa	Follow up ranged from 1	3778 adults with SSc-ILD (with signs of	Treatment: MMF	Patients who took MMF had severe baseline impairment of FVC and DLCO, which was even more pronounced when glucocorticoid was added to MMF. Values for DLCO and FVC

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
	al cohort study (EUSTAR)	tional study)	month to 13 years and available in 73.6% of those with SSc-ILD	ILD on HRCT or CXR) were observed from 2004 through 2014; 13.1% had ever taken MMF	Comparator: no immunosuppression (also reported other immunosuppressive medications; reported in other PICO summaries)	were lower and severe NYHA classification more frequent than in MMF monotherapy. Regarding DLCO trend, there was a negative multiplicative effect of MMF, meaning an even steeper decrease than the general trend vs positive multiplicative effect in patients in the never IS group. Adjusted for potential confounders and initial FVC or DLCO value no other medications than GCs, MMF, or "never IS" showed multiplicative effects on the course of lung function divergent from the general trend of the entire patient population. Observational study, high risk of confounding by indication.
Volkmann et al., 2017[3]	Double blinded RCT (combined data from SLS-1 placebo arm and SLS-2 MMF arm)	Low (RCT) however combined data from 2 separate RCTs for this analysis	1 year for placebo group (SLS-1), 2 years for MMF group (SLS-2)	69 MMF-treated patients and 79 placebo-treated patients with SSc-ILD	Treatment: MMF (of SLS-2; target dose 1500mg BID Comparator: placebo (of SLS-1)	In SLS II, 20 patients (29.0%) in the MMF arm prematurely stopped study drug treatment (due to 1 death, no treatment failures, and 19 withdrawals for other reasons) over 24 months. An additional 4 deaths in the MMF arm occurred in subjects who had already withdrawn for other reasons. In SLS I, during the initial 12 months, 24 patients (30.4%) in the placebo arm prematurely stopped study drug treatment (due to 3 deaths, 5 treatment failures, and 16 withdrawals for other reasons). Primary outcome: FVC % predicted: After controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF was associated with improved % predicted FVC over 24 months. The test of the overall treatment group effect for the entire model was highly significant (P = 0.0001). Using the intent-to-treat population, 64.4% and 71.7% of MMF-treated patients had any improvement in % predicted FVC at 12 and 24 months, respectively, and the majority of patients who experienced improvement in % predicted FVC at 24 months had an absolute improvement of >5%.

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
						Absolute (unadjusted) FVC change at 12 months in Rev Man. Secondary outcomes: <u>DLCO % predicted:</u> After controlling for baseline % predicted DLCO and baseline whole lung QILD score, treatment with MMF was associated with improved % predicted DLCO over 24 months (P = 0.0001). Absolute (unadjusted) DLCO change at 12 months in Rev Man. <u>TDI (transition dyspnea index):</u> After adjustment for baseline dyspnea index, treatment with MMF was associated with improvement in dyspnea compared with placebo as measured by the TDI (P = 0.0112). Absolute (unadjusted) TDI change at 12 months in Rev Man. <u>AEs</u>: Regarding any non-serious adverse event, there were 7 in the placebo arm and 23 in the MMF arm. (See Table 1). The breakdown of non-serious adverse events are as follows: (leukopenia (4 AEs in the MMF arm and none in the placebo arm), neutropenia (3 AEs in the MMF arm and none in the placebo arm), anemia (8 AEs in the MMF arm and 1 in the placebo arm), and pneumonia (5 AEs in the MMF arm and 1 in the placebo arm) occurred in more MMF-treated patients in SLS II than placebo-treated patients in SLS I. Note, there are limitations combining data from 2 trials to create the comparative arms, the inclusion criteria were similar between SLS-1 and SLS-2.
Matson et al., 2022[4]	Retrospective observational cohort	High	27.5 months	212 patients with RA-ILD	77 were treated with MMF, 92 treated with azathioprine,	In an analysis combining all three treatment agents, choice of immunosuppressive agent did not significant impact pulmonary function trajectory defined by FVC and DLCO change at 12-months.

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
					43 with rituximab	In the combined analysis of all three agents, there was an improvement in forced vital capacity (FVC) % predicted after 12 months of treatment compared to the potential 12-month response without treatment [+3.90%, p=< 0.001; 95% CI, (1.95, 5.84)]. Safety of MMF: 1. 3 of 77 patients discontinued MMF due to treatment related side effects. 2. Any adverse effect: 12 (16%) 3. GI upset 5 (6.5%) 4. Recurrent infection 2 (2.6%) 5. Cytopenia 2 (2.6%) 6. Elevated liver enzymes 0 7. Nonspecific symptoms 5 (5.4%)

6MWD: 6-minute walk distance

Table 25-3. PICO 25 Excluded Studies

Reference	Reason for Exclusion
Chen et al. 2022[5]	Not a comparator of interest
Highland et al. 2021[16]	Not a comparator of interest
Kelly et al. 2021[11]	Not a comparator of interest
Jaafar et al. 2021[8]	Not a comparator of interest
Amlani et al. 2020[13]	Not a comparator of interest
Kim et al. 2020[14]	Not a comparator of interest
Hoa et al. 2020[7]	Not a comparator of interest
Hanaoka et al. 2019[6]	Not a comparator of interest
Namas et al. 2018[9]	No outcome of interest.
Goldin et al. 2018[10]	Not a comparator of interest
Adler et al. 2018[12]	Duplicate to reference[2]
Tashkin et al. 2017[15]	Not a comparator of interest

References for PICO 25

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PICO 26: In rheumatic disease patients with ILD, what is the impact of cyclophosphamide compared to no cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low (systemic sclerosis); Very low (connective tissue disease)**

Key Findings:

- Tashkin et al., 2006,[1] a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006,[2] a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a non-statistically significant ($p=0.08$) trend towards improved FVC percent predicted adjusted for baseline FVC in the CYC group.
- Observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.[3,4,5,6,7,8]

Summary:

We found evidence to address this PICO from 2 randomized controlled clinical trials of low quality (Tashkin et al., 2006,[1] Hoyles et al., 2006[2]), 6 observational studies(Jensen et al., 2019,[3] Tzelepis et al., 2007,[4] Nakamura et al., 2021,[5] Adler et al., 2018, [6] Steen et al., 1994,[7] Fu et al., 2019[8]) and 8 follow-up studies(Furst et al., 2011,[9] Clements et al., 2007,[10] Strange et al., 2008,[11] Tashkin et al., 2007,[12] Theodore et al., 2012,[13] Goldin et al., 2009,[14] Kim et al., 2011,[15] Sindhwani et al., 2015[16]) of an RCT (Tashkin et al., 2006[1]).

Summary of 2 RCTs: Tashkin et al., 2006[1] is a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide (CYC) versus placebo in 158 scleroderma ILD patients presented in Table 26-1 and Table 26-2. This study met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$). Table I provides the analyses of unadjusted FVC, DLCO, TLC, SF36, and skin thickness showing statistically non-significant improvements in the CYC group, but a statistically significant improvement in HAQ scores. No statistically significant differences were observed with regard to serious adverse events, pneumonia, anemia, hematuria, and deaths, but the CYC did have a significantly higher rate of leukopenia. Table 26-2 is a summary of 8 studies that performed additional analyses on the original RCT. Important findings from these studies show that the change in FVC seen at 1 year, was not observed after 2 years. [12] Theodore et al., 2012[13] reported similar benefits in patients reporting cough at 1 year, but not 2 years. Clements et al., 2007[10] analyzed the change in

FVC in limited and diffuse SSc and observed a significant improvement in patients with limited disease, but not diffuse disease. Furst et al., 2011[9], reported an increase in total adverse events in the CYC group at year 1 (p=0.002), primarily driven by an increase in hematologic adverse events (p=0.001), in particularly leukopenia (p<0.0001). No differences were observed in the number of deaths between groups. Strange et al., 2008[11] reported that more patients with abnormal BAL had a response to CYC compared to placebo. Lastly, 3 studies reported improvements in high-resolution CT fibrosis scores through various methodologies in the CYC group compared to the placebo group. [14-16]

Hoyles et al., 2006[2] is a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo, in 45 scleroderma ILD patients, presented in Table 26-3. This trial demonstrated a statistically non-significant (p=0.08) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group compared to the placebo group at 12 months.

Summary of 6 observational studies (Table 26-4 **and** Table 26-5**):** Jensen et al., 2019 [3] reported on 12 patients with anti-synthetase syndrome ILD, with 7 patients treated with CYC and steroids compared to 2 patients treated with steroids alone. The CYC+steroids group had a statistically significant, larger improvement in FVC and DLCO compared to the steroids alone group. Tzelepis et al., 2007[4] reported on 59 patients with SSc-ILD, 29 treated with CYC v 30 not treated with CYC. Patients treated with CYC were more likely to have an improvement in FVC by at least 10% than no CYC (RR 4.14, 0.96-17.87). Adler et al., 2018[6] reported on the EUSTAR SSc cohort and reported no benefit of CYC in patients with DLCO < 50%; no other data were attributable to CYC versus no CYC. Lastly, Steen et al., 1994[7], reported on a cohort of 122 patients with SSc ILD. Individuals treated with CYC but no other immunosuppressants were the only group to show improvements in FVC% from baseline to the end of the study (P<0.05). However, there was an increase in non-pulmonary mortality. Nakamura et al., 2021[5] compared rheumatoid arthritis ILD patients with an acute exacerbation treated with steroids and CYC to propensity-matched RA-ILD acute exacerbations treated with steroids but not CYC. Results indicated no differences in mortality, discharging on oxygen, or duration of mechanical ventilation but showed higher rates of the need for platelet transfusions in patients treated with CYC. Fu et al., 2019 performed a Cox regression analysis of a retrospective cohort of RA-ILD patients and observed an improved survival in RA-ILD treated with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, P < 0.01).[8]

Table 26-1: PICO 26. Cyclophosphamide vs no cyclophosphamide as first-line treatment for systemic sclerosis associated ILD (RCT data)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	placebo, RCT	Relative (95% CI)	Absolute (95% CI)		
Change in TLC from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	serious[c]	serious[a, b]	none	79	79	-	MD 2.5 higher (1.77 lower to 6.77 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in DLCO from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	serious[c]	serious[a, b]	none	79	79	-	MD 0.7 lower (3.58 lower to 2.18 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in FVC from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	serious[c]	serious[a, b]	none	79	79	-	MD 1.6 higher (0.82 lower to 4.02 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in HAQ from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a]	none	79	79	-	MD 0.27 lower (0.42 lower to 0.12 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Change in SF36 Physical from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	79	79	-	MD 2.6 higher (0.33 lower to 5.53 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in SF36 Mental from baseline to 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	79	79	-	MD 2.8 higher (1.18 lower to 6.78 higher)	⊕⊕◯◯ Low	IMPORTANT
Total Serious Adverse Events (SAE)												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	20/79 (25.3%)	16/79 (20.3%)	RR 1.25 (0.70 to 2.23)	51 more per 1,000 (from 61 fewer to 249 more)	⊕⊕◯◯ Low	CRITICAL
SAE: related to treatment												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[c, d]	none	2/79 (2.5%)	0/79 (0.0%)	RR 5.00 (0.24 to 102.51)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Adverse Events: Hematuria												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	9/79 (11.4%)	3/79 (3.8%)	RR 3.00 (0.84 to 10.67)	76 more per 1,000 (from 6 fewer to 367 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	placebo, RCT	Relative (95% CI)	Absolute (95% CI)		
Adverse Event: Leukopenia												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a,b]	none	19/79 (24.1%)	0/79 (0.0%)	RR 39.00 (2.40 to 634.93)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL
Adverse Events: neutropenia												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a,b]	none	7/79 (8.9%)	0/79 (0.0%)	RR 15.00 (0.87 to 258.25)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL
Adverse Event: anemia												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	2/79 (2.5%)	1/72 (1.4%)	RR 1.82 (0.17 to 19.68)	11 more per 1,000 (from 12 fewer to 259 more)	⊕⊕◯◯ Low	CRITICAL
Adverse Event: Pneumonia												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	5/79 (6.3%)	1/79 (1.3%)	RR 5.00 (0.60 to 41.83)	51 more per 1,000 (from 5 fewer to 517 more)	⊕⊕◯◯ Low	CRITICAL
Deaths at 12 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	2/79 (2.5%)	3/79 (3.8%)	RR 0.67 (0.11 to 3.88)	13 fewer per 1,000 (from 34 fewer to 109 more)	⊕⊕◯◯ Low	CRITICAL
Deaths at 24 months												
Tashkin et al., 2006[1]	randomised trial	not serious	not serious	not serious	serious[a, b]	none	4/79 (5.1%)	3/79 (3.8%)	RR 1.33 (0.31 to 5.76)	13 more per 1,000 (from 26 fewer to 181 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
a. single study with <200 patients per arm, very few events
b. 95% CI includes the possibility of no difference
c. surrogate outcome for mortality

Table 26-2: PICO 26. Subgroup and follow up studies of RCT (Tashkin et al., 2007, Table 1) examining cyclophosphamide vs placebo in systemic sclerosis associated ILD

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Tashkin et al. 2007[12]	RCT	High	2 years	SSc-ILD	Oral cyclophosphamide versus oral placebo	Change in FVC in SLSI 2 years (follow-up: 24 months; assessed with: change in FVC at 2 years) 57 CYC and 56 placebo completed 2 years · A benefit in FVC% and TLC% was observed at 12 and 18 months. · No positive effect in FVC% and TLC% was observed at 24 months.
Clements et al. 2007[10]	RCT	High	1 year	Limited SSc and Diffuse SSc with ILD	Oral cyclophosphamide versus oral placebo	Change in FVC in diffuse v limited SSc (follow-up: 12 months; assessed with: Change in FVC): Patients with Limited SSc (55) v Diffuse SSc (90) CYC v placebo had a statistical decrease in the decline in FVC% in the LSSc group (-0.17+/- 1.47 v -3.49+/-.95, p=0.03). CYC v placebo had a NON statistical decrease in the decline in FVC% in the dSSc group (-0.35+/-0.98 v -1.8+/-1.2, p=0.39).
Theodore et al. 2012[13]	RCT	High	1 year	SSc-ILD	Oral cyclophosphamide versus oral placebo	Cough (follow-up: 24 months; assessed with: Cough survey) In the placebo group, 68% of patients had cough at baseline and at 1 year. In the CYC group 71% of patients had cough at baseline and 56% at 1 year. There was no difference at 2 years.
Furst et al. 2011[9]	RCT	Moderate	1 and 2 years	SSc-ILD	Oral cyclophosphamide versus oral placebo	AE in SLS I (follow-up: 24 months; assessed with: 2-year observation after RCT) CYC had an increase in total adverse events not including death or cancer (154 AE in 54 patients (67%) v 60 AE in 21 patients (26%) p=0.002). The largest difference was seen in hematologic AE (CYC 33 events in 21 (26%) patients, Placebo 2 events in 2 patients (2%), p=0.001). Leukopenia was more common in CYC than placebo (19 in CYC, 0 in placebo, p<0.0001).

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
						No difference in AE at year two were seen. Hematuria was numerically but not statistically more common in CYC group than placebo (9.9% v 4.9%, p=0.37). Deaths in SLSI at 24 months: 12 total deaths observed 1 death attributed to CYC 1 death from placebo "related to test substance" and related to infection 10 deaths "unrelated to test substance".
Strange et al. 2008 [11]	RCT	Moderate	1 year	SSc-ILD with normal or abnormal BAL (abnormal cellularity (<3%PMN or >2% eos)	Oral cyclophosphamide versus oral placebo	<u>Change in FVC in patients with abnormal BAL or normal BAL (follow-up: 12 months; assessed with: change in FVC)</u> 126 of the 158 randomized patients were analyzed. · Abnormal cellularity (<3%PMN or >2% eos) was not an independent predictor of response to cyclophosphamide (p=0.075) as defined by a change in FVC from baseline. In the BAL+ group more patients who received cyclophosphamide had a stabilization of FVC than those who received placebo (p=0.034), but not in the BAL- group (p=0.42).
Goldin et al. 2009[14]	RCT	High	1 year	SSc-ILD	Oral cyclophosphamide versus oral placebo	<u>HRCT outcomes at 1 year (assessed with HRCT fibrosis, GGO, honeycomb cyst)</u> 98 patients were analyzed based on available HRCT. · Fibrosis score worsened in the placebo group more than the CYC group (p-0.014). In CYC group, 14 worsened, 35 no change in FIB. In the placebo group 26 worsened and 23 not worse. · No changes in ground glass or honeycomb cysts
Kim et al. 2011[15]	RCT	High	1 year	SSc-ILD	Oral cyclophosphamide versus oral placebo	<u>HRCT Quantitative lung fibrosis (QLF) (follow-up: 12 months; assessed with: QLF)</u> 83 patients were analyzed based on available HRCT. · In the zones with the highest zonal score at baseline, QLF scores in the CYC decreased by a mean of 2.6% compared to an increase of 9.1% in the placebo group (p=0.0027).

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
						· In the whole lung, changes in QLF in the CYC group were different than placebo (p=0.019). 59% of CYC patients had a decrease in QLF compared to only 26% of placebo in the whole lung.
Kim et al. 2016[17]	RCT	High	1 year	SSc-ILD	Oral cyclophosphamide versus oral placebo	HRCT Computer aided analyses QILD (follow-up: 12 months; assessed with: Computer aided analysis): 83 patients with SSc ILD with 2 serial HRCT were analyzed. · The QILD score in most severe zone decreased 3.9% in the CYC group and increased by 4.2% in the placebo group (p=0.01). · Whole lung QILD decreased 3.2% in CTC group and increased 2.2% in placebo group (p=0.03). · 60% of CYC patients had decreasing or stable QILD scores vs 67% of placebo group showing increased QILD scores in the most severe zone (similar in whole lung also).

Table 26-3: PICO 26. Cyclophosphamide vs no cyclophosphamide as first-line treatment for systemic sclerosis associated ILD (RCT data not in RevMan)

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Hoyles et al. 2006[2]	RCT	High[a]	1 year	SSc-ILD	6 months IV CYC followed by azathioprine maintenance versus placebo	Change in FVC at 12 months adjusted for baseline (data not presented similar to SLSI). 45 patients., 22 CYC-AZA, 23 placebo, only 19 and 18 analyzed, · FVC% in CYC group: pre 80.1 +/- 10.3, post 82.5 +/- 11.3 · FVC% in placebo group: pre 81.0+/- 18.8, post 78.0 +/- 21.6 · Primary outcome CYC-AZA had a better change in FVC% than placebo, but did not meet statistical significance (p=0.08) Serious adverse events were similar between groups.

[a]Not all patients randomized were analyzed

Table 26-4: PICO 26. Cyclophosphamide vs no cyclophosphamide as first-line treatment for connective tissue disease associated ILD (data from observational studies)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	No CYC	Relative (95% CI)	Absolute (95% CI)		
Change in FVC% from baseline to study end (cohort)												
Jensen et al., 2019 [3]	observational studies, antisynthetase syndrome ILD	serious[a]	not serious	serious[d]	very serious[b,c]	all plausible residual confounding would reduce the demonstrated effect	7	2	-	MD 5.57 higher (9.37 lower to 20.51 higher)	⊕◯◯◯ Very low	IMPORTANT
Change in DLCO% from baseline to end study (cohort)												
Jensen et al., 2019 [3]	observational studies, antisynthetase syndrome ILD	serious[a]	not serious	serious[d]	very serious[b]	all plausible residual confounding would reduce the demonstrated effect	7	2	-	MD 19.5 higher (8.08 higher to 30.92 higher)	⊕◯◯◯ Very low	IMPORTANT
FVC improvement in CYC v untreated												
Tzelepis et al., 2007 [4]	observational studies, systemic sclerosis associated ILD	serious[a]	not serious	serious[d]	very serious[b]	all plausible residual confounding would reduce the demonstrated effect	8/29 (27.6%)	2/30 (6.7%)	RR 4.14 (0.96 to 17.87)	209 more per 1,000 (from 3 fewer to 1,000 more)	⊕◯◯◯ Very low	IMPORTANT
Mortality at 90 days												
Nakamura et al., 2021 [5]	observational studies, rheumatoid arthritis associated ILD	serious[a]	not serious	not serious	very serious[c,b]	all plausible residual confounding would reduce the demonstrated effect	60/129 (46.5%)	218/516 (42.2%)	RR 1.10 (0.89 to 1.36)	42 more per 1,000 (from 46 fewer to 152 more)	⊕◯◯◯ Very low	CRITICAL
Discharge on oxygen												
Nakamura et al., 2021[5]	observational studies, rheumatoid arthritis associated ILD	serious[a]	not serious	not serious	very serious[c,b]	all plausible residual confounding would reduce the demonstrated effect	11/129 (8.5%)	43/516 (8.3%)	RR 1.02 (0.54 to 1.93)	2 more per 1,000 (from 38 fewer to 77 more)	⊕◯◯◯ Very low	CRITICAL
Duration of mechanical ventilation												
Nakamura et al., 2021 [5]	observational studies, rheumatoid arthritis associated ILD	serious[a]	not serious	not serious	very serious[c,b]	all plausible residual confounding would reduce the demonstrated effect	129	516	-	MD 4.5 higher (0.85 lower to 8.15 higher)	⊕◯◯◯ Very low	CRITICAL
Need for platelet transfusion												
Nakamura et al., 2021[5]	observational studies, rheumatoid arthritis associated ILD	serious[a]	not serious	not serious	very serious[c,b]	all plausible residual confounding would reduce the demonstrated effect	9/129 (7.0%)	12/516 (2.3%)	RR 3.00 (1.29 to 6.97)	47 more per 1,000 (from 7 more to 139 more)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	No CYC	Relative (95% CI)	Absolute (95% CI)		
Number of patients with sepsis												
Nakamura et al., 2021[5]	observational studies, rheumatoid arthritis associated ILD	serious[a]	not serious	not serious	very serious[a,b]	all plausible residual confounding would reduce the demonstrated effect	6/129 (4.7%)	16/516 (3.1%)	RR 1.50 (0.60 to 3.76)	16 more per 1,000 (from 12 fewer to 86 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. patients were not randomized to CYC or placebo/no CYC
b. single study with less than 50 per arm
c. 95%CI includes line of no difference
d. surrogate outcome for mortality

Table 26-5: PICO 26. Cyclophosphamide vs no cyclophosphamide as first-line treatment for connective tissue disease associated ILD (data from observational studies, not in RevMan)

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Adler et al. 2018 [6]	Observational	High	3 months to 20 years	EUSTAR SSc-ILD Cohort	CYC vs no CYC	CYC was used in more severe cases of SSc ILD including patients with worse lung function (FVC% and DLCO%) and the highest rates of ground glass opacification on imaging and the most severe skin score (mRSS). The use of CYC did not alter the SScILD course in those patients with DLCO% <50% (CYC effect not reported for others).
Steen et al. 1994[7]	Observational	High	4 months to 3 years	A retrospective cohort study of 122 SSc-ILD patients (2 abnl PFTs).	Groups studies: 21 high dose steroids, 16 immunosuppressant not CYC, 14 Cyclophosphamide, and 37 D-penicillamine and 34 no medications.	At baseline, CYC had more frequent severe dyspnea ($p<0.05$). CYC was the only group to show an improvement in FVC% from baseline to end of study ($p<0.05$) and had a mean improvement of 435 ml/year in FVC ($p<0.005$ by ANOVA). DLCO change not consistent. CYC and immunosuppressives other than CYC had the worse overall survival, but half of CYC treated deaths were non-pulmonary.
Fu et al. 2019[8]	Retrospective cohort, 2008-2014	High	51.02 months (range 2.66–104.79 months).	266 RA-ILD patients followed in Chao-Yang Hospital, Capital Medical University in China.	Treatments: cyclophosphamide, methotrexate and tripterygium	During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. In multivariable Cox regression analyses, treatment with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, P < 0.01) was associated with better survival.

Table 26-6. PICO 26 Excluded studies

Reference	Reason for Exclusion
Perez-Campos et al. 2012[18]	Not a comparator of interest
Hoa et al. 2020 [19]	Not a comparator of interest

Reference	Reason for Exclusion
Behr et al. 1996 [20]	Not a comparator of interest
Lu et al. 2018 [21]	Not a comparator of interest
Kundu et al. 2016 [22]	Not a comparator of interest
Li et al. 2019 [23]	Wrong population
Namas et al. 2018 [24]	No outcome of interest
Bodolay et al. 2005 [25]	No outcome of interest
Ciaffi et al. 2020 [26]	Not a comparator of interest
Ciaffi et al. 2022 [27]	Duplicate study
Hoa et al. 2020 [19]	No outcome of interest
Grau et al. 1996[28]	No outcome of interest
Friedman et al. 1996 [29]	No outcome of interest
Airo et al. 2007 [30]	Not a comparator of interest
Davas et al. 1999 [31]	Not a comparator of interest
Bruni et al. 2020 [32]	Not a comparator of interest
Domiciano et al. 2011 [33]	Not a comparator of interest
Tsuji et al. 2020[34]	Not a comparator of interest
Shi et al. 2009 [35]	Not a comparator of interest
Okamoto et al. 2016 [36]	No outcome of interest
Kelly et al. 2021 [37]	Not a comparator of interest
Chen et al. 2022 [38]	Not a comparator of interest
Adler et al. 2018 [38]	Duplicate study [6]
Kim et al. 2020[39]	Not a comparator of interest

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PICO 27: In rheumatic disease patients with ILD, what is the impact of leflunomide compared to no leflunomide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings

- One single-center retrospective cohort study assessed the risk of infection of patients receiving methotrexate/Leflunomide (n=54) vs no therapy (n=48). The infection rate in the MTX/LEF group vs no therapy group was 7.4 vs 6.6 per 100 patient years (PY), respectively.
- A multicenter prospective observational cohort study of RA-ILD patients exposed to either LEF, MTX, or TAC demonstrated that LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, p=0.031 and an increased risk of ILD progression in patients with decreased lung function (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression and were at higher risk for ILD progression.

Summary:
We included two studies that addressed this PICO question.

Zamora-Legoff et al. 2016[1] assessed the rate of infection in RA-ILD patients who received various forms of immunosuppression. Of the 181 patients in the study, 54 received a combination of MTX/Leflunomide and 48 received no therapy, providing the basis for our assessment. Since patient receiving MTX or LEF were lumped together in this study, direct conclusions regarding the impact on LEF specifically are difficult to draw, so the evidence is of very low quality. The infection rate per 100 PY in the MTX/LEF was 7.4 vs. 6.6 for the No Therapy group.

A multicenter prospective observational cohort study[2] included 143 RA-ILD patients, of which 26 (18.2%) were exposed to LEF. Multivariable Cox regression analysis was performed to determine factors associated with RA-ILD progression. LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, p=0.031) and an increased risk of ILD progression in patients with decreased lung function defined as and FVC < 70% or DLCO < 60% (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression (median time to progression, 29.3 vs 44.2 months; log-rank, P= 0.049) and were at higher risk for ILD progression (adjusted HR, 2.56; 95% CI, 0.93, 7.06).

Table 27-1: Leflunomide compared to no leflunomide as first line ILD treatment

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Zamora-Legoff et al. 2016[1]	Retrospective cohort study	High	Risk of infection analyzed by person-year methods using time-dependent covariates started when med first used up until 30 days after stopping	RA-ILD patients seen at Mayo Clinic Exclusion criteria: patients with concomitant rheumatological disease (except for secondary SS)	48 patients on no therapy 54 patients on MTX/LEF	Infection rates: 7.4 per 100 PY with MTX/LEF vs. 6.6 per 100 PY with no therapy.
Kim et al. 2022[2]	Prospective observational cohort study	High		RA-ILD patients	143 RA-ILD patients exposed to either MTX (n-61), LEF (n=26), or TAC (n=56)	At baseline, 64 patients had ILD progression (16 (25%) were given LEF. Of 79 patients without ILD progression, 10 (12.7%) were given LEF. Events (RA-ILD progression)/population No LEF 48/117 (41%) LEF 16/26 (61.5%) Cox regression analysis for RA-associated ILD progression LEF use 1.75 (0.88, 3.46) p=0.109

Table 27-2. PICO 27 Excluded Studies

Reference	Reason for Exclusion
Chen et al. 2022[3]	No outcome of interest

References

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

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PICO 28: In rheumatic disease patients with ILD, what is the impact of methotrexate compared to no methotrexate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- 3 observational studies of 381 RA-ILD patients reported that 60 (30.6%) patients classified as "progressive," and 71 (38.3%) patients classified as "stable" were taking methotrexate.[1-3]
- 1 observational study reported that treatment with MTX, LEF, and tacrolimus were not associated with progression of RA-ILD.[3]
- 1 observational study reported that treatment with MTX was not associated with better survival (HR 0.58, 95% CI: 0.33 to 1.01).[1]

Summary:

Three studies addressed this PICO question. [1-3]

Chen et al., 2022[2] conducted a retrospective cohort study to identify the characteristics of RA-ILD patients on progression and prognosis. 75 cases were included, of whom 32 were classified as progressive (defined as a decrease of FVC >10% or DLCO >15% predicted), and 43 were classified as stable. Among the progressive RA-ILD group, 5/32 (15.6%) were on methotrexate (MTX); among the stable group, 5/43 (11.6%) were taking MTX.

Kim et al., 2022[3] conducted a prospective cohort study to examine the association between MTX, LEF, and tacrolimus use and the progression of ILD among 143 patients with RA-associated ILD. Of the 143 patients, 64 (44.7%) patients experienced ILD progression (MTX use: 27/61 (42.2%) during a median follow-up period of 33 months). ILD progression was defined when patients exhibited ≥1 of the following during the follow-up period: (i) a decrease of ≥10% in FVC; (ii) a decrease of ≥15% in DLco; or (iii) death from respiratory failure due to ILD and/or pneumonia. The use of MTX [adjusted hazard ratio (aHR), 1.06; 95% CI, 0.59, 1.89], LEF (aHR, 1.75; 95% CI, 0.88, 3.46) and tacrolimus (aHR, 0.94; 95% CI, 0.52, 1.72) did not increase the risk of ILD progression. However, the association between LEF use and the risk of ILD progression was significant in subgroups with poor lung function (aHR, 8.42; 95% CI, 2.61, 27.15). Older age, male sex, a shorter RA duration, higher RA disease activity and extensive disease at baseline were independently associated with ILD progression.

Evidence for ILD progression was also provided by Fu et al., 2019[1], a retrospective cohort study in China conducted from May 2008 to January 2014 (n=266). The outcomes of interest were 1) ILD progression defined as: a decrease of FVC > 10% or DLCO > 15% predicted, worsening of ILD or death from respiratory failure due to ILD and/or pneumonia; and 2) survival. The median observation period was 51.02 months (range 2.66–104.79 months).

The 3-year survival rate was 81.24%, and the 5-year survival rate was 69.71%. During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. 103 RA-ILD patients experienced ILD progression, and 81 were stable (see Table 28-1 for combined data for both studies). Methotrexate (MTX) use had an OR of 0.72 (95% CI 0.25-2.08) for RA-ILD progression in multivariable logistic regression. In multivariable Cox regression analyses, the HR for MTX use with survival was 0.58 (0.33-1.01) (Table 28-2). Treatment with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, P < 0.01) was associated with better survival.

Table 28-1:PICO 28: MTX vs no MTX in RA-ILD patients

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX use, progressive	stable RA-ILD	Relative (95% CI)	Absolute (95% CI)		
RA-ILD progression												
3 Chen et al., 2022[2], Kim et al., 2022[3], Fu et al., 2019[1]	observational studies	very serious[a]	not serious	serious[b]	serious[c]		60/196 (30.6%)	71/185(38.3%)	RR 0.79 (0.60 to 1.06)	77 fewer per 1,000 (from 154 fewer to 19 more)	⊕⊕⊕◯ Very Low	Important

CI: confidence interval; **RR:** risk ratio

Explanations

a. Retrospective, small studies

b. Surrogate outcome for mortality

c. 95% CI includes the line of no difference

Table 28-2:PICO 28: Methotrexate vs no methotrexate in RA-ILD patients

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment and Comparator	Results
Chen et al. 2022[2]	Retrospective cohort, Oct 2010- Sep 2020	High, retrospective, small study	Pulmonary functional impairment compared with the diagnosis of baseline time, assessed by changes of HRCT score of PFT during follow-up	RA-ILD patients seen at Changhai Hospital (The Second Military Medical University in China) were divided into "progressive group" (n=32) and "stable group" (n=43)	Steroids, LEF, MTX, CYC/MMF, TNFi	Among the progressive RA-ILD group, 5/32 (15.6%) were on methotrexate and among the stable group, 5/43 (11.6%) were taking MTX. Note: data included in GradePro file.
Kim et al. 2022[3]	Prospective cohort, patients enrolled Jan 2015-June 2018 Conducted in Korea	Some concerns, small study; differences in duration of age, RA enrollment, HRCT pattern, and predicted DLCo	≥3 years with last follow-up in Sept 2021	168 patients with rheumatoid arthritis associated ILD Age: 66.3 (8.1) % Male: 33.6 Extent of ILD: Limited disease (79%); extensive disease (21.0%)	**Medications during follow-up**: Glucocorticoid: 87.4% Methotrexate (MTX): 42.7% Leflunomide (LEF): 18.2% Tacrolimus (TAC): 39.2% Other DMARDs: 32.9%	ILD progression was defined when patients exhibited ≥1 of the following during the follow-up period: (i) a decrease of ≥10% in FVC; (ii) a decrease of ≥15% in DLco; or (iii) death from respiratory failure due to ILD and/or pneumonia. Patients with ILD progression: n=64, MTX: 42.2%, LEF: 25.0%; TAC: 34.4 Patients without ILD progression: n=79, MTX: 43.0%, LEF: 12.7%, TAC: 43.0% Adjusted hazard ratio for progression: MTX aHR, 1.06; 95% CI, 0.59, 1.89, no association with progression LEF: aHR, 1.75; 95% CI, 0.88, 3.46), no association with progression LEF use and the risk of ILD progression was significant in subgroups with poor lung function (aHR, 8.42; 95% CI, 2.61, 27.15).

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment and Comparator	Results
						TAC: aHR, 0.94; 95% CI, 0.52, 1.72) no association Older age, male sex, a shorter RA duration, higher RA disease activity and extensive disease at baseline were independently associated with ILD progression.
Fu et al. 2019[1]	Retrospective cohort, 2008-2014	High	51.02 months (range 2.66–104.79 months).	266 RA-ILD patients followed in Chao-Yang Hospital, Capital Medical University in China.	Treatments: cyclophosphamide, methotrexate and tripterygium	During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. In multivariable Cox regression analyses, the HR for MTX use with survival was 0.58 (0.33-1.01).

Table 28-3. PICO 28 Excluded Studies

Reference	Reason for exclusion
Jaafar et al. 2021[4]	No comparator of interest
Maher et al. 2022[5]	No comparator of interest
Volkmann et al. 2022[6]	No intervention of interest
Maher et al. 2020[7]	No intervention of interest
Assassi et al. 2022[8]	No intervention of interest
Maher et al. 2022[9]	No intervention of interest
Azuma et al. 2021[10]	No intervention of interest
Inoue et al. 2021[11]	No intervention of interest
Liang et al. 2021[12]	No intervention of interest
Schmid et al. 2021[13]	No intervention of interest
Kreuter et al. 2022[14]	Wrong study design
Tille-Leblond et al. 2008[15]	Wrong study design
Cottin et al. 2021[16]	No intervention of interest
Distler et al. 2019[17]	No intervention of interest

Reference	Reason for exclusion
Zamore-Legoff et al. 2016[18]	No intervention of interest
Seibold et al. 2020[19]	No intervention of interest

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PICO 29: In rheumatic disease patients with ILD, what is the impact of azathioprine compared to no azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate benefit of AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.
- One RCT (Nadashkevich et al., 2006[13]) comparing combination prednisone with CYC or AZA in 60 individuals with SSc indicated a significant worsening in FVC % predicted (mean±SD: -11.1±1.0 AZA, 3.3±0.7 CYC; p<0.001) and DLCO % predicted (mean±SD: -11.6±1.3 AZA, 0±1.6 CYC; p<0.001) with AZA vs CYC at 18 months follow-up. Authors reported that "no life-threatening or irreversible adverse reactions" were observed with either treatment.

Summary:

We included two randomized controlled trials (RCTs) (Hoyles et al., 2006,[1] Nadashkevich et al., 2006[13]) and three observational studies (Amlani et al., 2020,[2] Kaenmuang et al., 2020,[3] and Matson et al., 2022[4]) that addressed this PICO question.

Results from RCTs:

In a single double-blind RCT, 45 SSc patients with early pulmonary fibrosis (median age 55, 71% women) were treated with either PO prednisolone 20 mg on alternate days and 6 IV infusions of CYC at a dose of 600 mg/m^2 (mean dose 1,050 mg) at 4-week intervals followed by PO AZA at 2.5 mg/kg/day (max 200 mg/day) versus placebo (with similar modalities of IV and PO administration).[1] Patients with a significant drop in their FVC or DLCO could switch into the treatment arm, but intention-to-treat

(ITT) analyses were performed. Subjects were followed for one year; however, only 25 patients completed the trial. In addition, 8 patients (including 5 in the placebo arm) were lost to follow-up. No statistically significant differences were noted in FVC and DLCO % predicted changes over time, although there was a favorable trend in FVC % predicted among patients in the treatment arm (FVC % predicted improved slightly in the treatment arm, whereas FVC % predicted decreased slightly in the placebo arm, p=0.08). This study only indirectly addresses PICO 29 since the intervention was a multimodal treatment plan. The study's limited sample size, significant loss to follow-up, and use of a surrogate outcome (PFTs) limit the ability to draw meaningful conclusions about the utility of azathioprine versus no azathioprine as first-line CTD-ILD treatment (Table 29-1).

One RCT (Nadashkevich et al., 2006[11]) comparing combination prednisone with CYC or AZA in 60 individuals with SSc indicated a statistically significant worsening in FVC % predicted (mean±SD: -11.1±1.0 AZA, 3.3±0.7 CYC; p<0.001) and DLCO % predicted (mean±SD: -11.6±1.3 AZA, 0±1.6 CYC; p<0.001) with AZA vs CYC at 18 months follow-up. Authors reported "no life-threatening or irreversible adverse reactions" were observed with either treatment.

Results from observational studies:

Only three observational studies provided low-quality evidence addressing PICO 29 with findings summarized in Table 2. Notably, one pSS-ILD study included only 7 patients on AZA and 5 patients receiving no treatment with no differences noted in FVC and DLCO % predicted slope changes before and after initiation of treatment.[2]

Another study looked across several clinical covariates (including being prescribed AZA) to see which were associated with progressive SSc-ILD.[3] For AZA, the unadjusted OR was 2.55 (95% CI 0.61-10.62). Given the wide confidence interval and the fact that patients could be on any other therapies not directly specified, these data provide very low-quality evidence addressing PICO 29.

Lastly, one study[4] showed that among patients taking AZA, MMF, and RTX, FVC% predicted was highest for MMF (4.55%), then AZA (3.84%) and RTX (3.26%), while DLCO% predicted was highest for RTX (6.73%), then MMF (3.67%) and AZA (1.93%). The adverse events were highest in AZA (19.6%), then MMF (15.6%) and RTX (11.6%).

Table 29-1: PICO 29: azathioprine vs no azathioprine: Key findings from RCT comparing azathioprine+prednisolone+CYC to placebo for first line ILD treatment

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine+prednisolone+CYC	placebo	Relative (95% CI)	Absolute (95% CI)		
Primary endpoints: change in FVC and DLCO % predicted; secondary endpoints: change in dyspnea scores (modified ATS respiratory questionnaire)												
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[a, c]	serious[b]	none	One-year multicenter, prospective, randomized, double-blind, placebo-controlled trial; patients with significant drop in FVC or DLCO could switch study arm, but analysis performed as ITT; 8 patients lost to follow-up, but ITT analysis was performed 45 SSc patients with early pulmonary fibrosis, median age 55, 71% women Intervention: PO prednisolone 20 mg on alternate days and 6 IV infusions of CYC at a dose of 600 mg/m2 (mean dose 1,050 mg) at 4-week intervals, followed by PO AZA at 2.5 mg/kg/day (max 200 mg/day) vs. placebo with same modality of administration FVC % predicted values: Tx: 80.1 (10.3) -> 82.5 (11.3) Placebo: 81.0 (18.8) -> 78.0 (21.6) p=0.08 DLCO % predicted values: Tx: 52.9 (11.5) -> 49.6 (10.7) Placebo: 55.0 (12.9) ◊ 51.8 (14.9) p=0.64 Dyspnea score Tx: 7.7 (2-14) -> 8.8 (0-14) Placebo: 7.2 (0-18) ◊ 7.8 (2-14) p=0.23				⊕⊕◯◯ Low	Important
Serious adverse events in RCTs - Intercurrent respiratory tract infections												
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[c]	very serious[d, e, f]		3/22 (13.6%)	4/23 (17.4%)	RR 0.78 (0.20 to 3.11)	38 fewer per 1,000 (from 139 fewer to 367 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in RCTs - Hospital admissions												
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[c]	very serious[d, e, f]		0/22 (0.0%)	1/23 (4.3%)	RR 0.35 (0.01 to 8.11)	28 fewer per 1,000 (from 43 fewer to 309 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in RCTs - Hematuria												
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[c]	very serious[d, f]		10/22 (45.5%)	6/23 (26.1%)	RR 1.74 (0.76 to 3.98)	193 more per 1,000 (from 63 fewer to 777 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in RCTs - Study discontinuation (dropout)												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine+prednisolone+CYC	placebo	Relative (95% CI)	Absolute (95% CI)		
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[c]	serious[b,d]		7/22 (31.8%)	10/23 (43.5%)	RR 0.73 (0.34 to 1.58)	117 fewer per 1,000 (from 287 fewer to 252 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in RCTs - Malignancies (any)												
Hoyles et al. 2006[1]	randomised trials	not serious	not serious	serious[c]	serious[b,d, e]		1/22 (4.5%)	1/23 (4.3%)	RR 1.05 (0.07 to 15.70)	2 more per 1,000 (from 40 fewer to 639 more)	⨁◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

a. surrogate outcome for mortality
b. single study, doesn't meet optimal information size
c. indirect comparison
d. 95% CI includes the line of no difference
e. very few events
f. single study, <50 patients

Table 29-2a: Summary of clinical outcomes data in observational studies

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Amlani et al. 2020[2]	Retrospective cohort study	High	Slope in FVC and DLCO % predicted plotted 12 months before and 12 months after treatment initiation	19 patients with pSS-associated ILD; AZA group (*n*=7): 86% female, mean age 57.7; MMF group (*n*=7): 71% female, mean age 58.9; RTX group (*n*=6): 83% female, mean age 55.7; no treatment group (*n*=5): 100% female, mean age 69.6 Inclusion criteria: ≥18 years old with pSS diagnosis and had clinically confirmed ILD Exclusion criteria: Another autoimmune disease present	AZA vs. MMF vs. RTX vs. no treatment (doses not specified)	Compared pre- and post-treatment slopes for FVC and DLCO % predicted determined by linear effects models FVC % predicted slope change before AZA: 1.5 (SD 11.4); slope change after AZA: 4.3 (SD 7.6); *p*=0.13 DLCO % predicted slope change before AZA: 0 (only 1 patient with recorded DLCO value); slope change after AZA: -0.3 (SD 4.5); *p*=0.96 **Adverse events summarized in Table 3**
Kaenmuang et al. 2020[3]	Retrospective cohort study	High	Baseline, 6-month, and 12-month PFTs and HRCT	78 patients with SSc-ILD, 83% female, mean age 44.7 Inclusion criteria: 1) >15 years old; (2) diagnosed with SSc according to the criteria described in the 2013 EULAR/ACR or the 1980 ACR classification criteria for SSc for patients diagnosed before 2013 by rheumatologists; and (3) diagnosed as SSc-ILD by pulmonologists	Treatment: AZA (dose not specified) Comparator: no AZA (but could be on any other therapies, which are not directly specified)	Participants who had lung function decline, defined as a decrease of FVC ≥10% and/or DLCO ≥15% within 1 year after initial diagnosis of SSc-ILD, were identified as progressive SSc-ILD Progressive SSc-ILD: 5/17 (29.4%) on AZA; stable SSc-ILD: 8/61 (13.1%) on AZA; *p*=0.143 AZA crude OR for progressive SSc-ILD: 2.55 (0.61-10.62), *p*=0.225 (i.e., use of AZA was not associated with ILD progression at 12 months of follow-up)

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
				according to the European Respiratory Society review 2015		
Matson 2022[4]	Retrospective cohort study	High	The median follow-up time was 27.5 months	212 patients diagnosed with RA-ILD	Initial treatments with Azathioprine vs. Mycophenolate vs. Rituximab	FVC % predicted at 12 months: Azathioprine 3.84%; Mycophenolate 4.55%; Rituximab 3.26% DLCO % predicted at 12 months: Azathioprine 1.93%; Mycophenolate 3.67%; Rituximab 6.73% **Adverse events:** All AE: Azathioprine 18 (19.6%); Mycophenolate 12 (15.6%); Rituximab 5 (11.6%) GI upset: Azathioprine 3 (3.3%); Mycophenolate 5 (6.5%); Rituximab 1 (2.3%) Elevated liver enzymes: Azathioprine 3 (3.3%); Mycophenolate 0 %; Rituximab 0 Cytopenia: Azathioprine 3 (3.3%); Mycophenolate 2 (2.6%); Rituximab 1 (2.3%) Recurrent infections: Azathioprine 4 (4.3%); Mycophenolate 2 (2.6%); Rituximab 1 (2.3%) Non-specific symptoms: Azathioprine 5 (5.4%); Mycophenolate 3 (3.9%); Rituximab 2 (4.7%)

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						Treatment stopped due to adverse event: Azathioprine 12 (13.0%); Mycophenolate 3 (3.9%); Rituximab 1 (2.3%).

Table 29-2b: Summary of clinical outcomes data in randomized trials

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Nadashkevich et al. 2006	RCT, unblinded	Low	18 months	Early diffuse SSc	Oral cyclophosphamide (CYC) (2 mg/ kg daily for 12 months, then 1 mg/kg daily) (n=30) vs oral azathioprine (AZA) (2.5 mg/kg daily for 12 months, then 2 mg/kg daily for 18 months)(n=30). Prednisone was also administered (15 mg daily and tapered to zero by end of the 6th month).	**FVC % predicted** **Mean (SD) change at 18 months:** -11.1±1.0 AZA, 3.3±0.7 CYC; p<0.001) **AZA:** Baseline: 91.7±2 6 months: 87.3±1.8 12 months: 83.6±1.9 18 months: 80.6±2.1 Versus baseline, AZA significant worsening at all time points **CYC:** Baseline: 90.3±1.9 6 months: 92.5±1.6 12 months: 91.8±1.8 18 months: 93.6±1.7 CYC increased over time (not significant) DLCO % predicted: **Mean (SD) change at 18 months:** -11.6±1.3 AZA, 0±1.6 CYC; p<0.001 AZA:

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						Baseline: 84.8±1.4 6 months: 80.2±1.9 12 months: 76.7±1.5 18 months: 73.2±1.6 Versus baseline, significant worsening at 12 and 18 months. CYC: Baseline: 83.5±1.6 6 months: 82.6±2.0 12 months: 83.1±1.7 18 months: 83.5±1.6 Versus baseline, no significant differences at all followups. Adverse events: "No life-threatening or irreversible adverse reactions were observed in either group."

Table 29-3: Summary of adverse events found in observational studies comparing azathioprine to no azathioprine for first-line ILD therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	no treatment	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events in observational studies - Drug discontinuation												
Amlani, B. et al., 2020[2]	observational studies	serious[a]	not serious	not serious	very serious[b, c, d]		2/7 (28.6%)	0/5 (0.0%)	**RR 3.75** (0.22 to 64.56)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	no treatment	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events in observational studies - Malignancies (any)												
Amlani, B. et al., 2020[2]	observational studies	serious[a]	not serious	not serious	very serious[b,c,d]		1/7 (14.3%)	1/5 (20.0%)	**RR 0.71** (0.06 to 8.90)	**58 fewer per 1,000** (from 188 fewer to 1,000 more)	⨁◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

a. retrospective cohort study
b. single study, <50 patients
c. very few events
d. 95% CI includes the line of no difference, wide CIs

Table 29-5: PICO 29 Excluded Studies

Reference	Reason for Exclusion
Jensen et al. 2019[5]	Wrong study design
Tillie-Leblond et al. 2008[6]	Wrong study design
Deheinzelin et al. 1996[7]	Wrong study design
Grau et al. 2996[8]	Wrong study design
Friedman et al. 1996[9]	Wrong study design
Okamoto et al. 2016[10]	No intervention of interest
Kelly et al. 2021[11]	No population of interest
Adler et al. 2018[12]	No outcome of interest

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PICO 30: In rheumatic disease patients with ILD, what is the impact of calcineurin inhibitors compared to no calcineurin inhibitors as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Two observational studies demonstrated the benefit of initiating a calcineurin inhibitor in combination with prednisolone as opposed to prednisolone alone as first-line therapy for IIM-ILD.
- Two observational studies present clinical outcomes data for complex treatment regimens with and without tacrolimus. Because of the multifaceted nature of these regimens, these studies do not directly address PICO 30.
- One observational study comparing the association of drug use on ILD progression showed insignificant differences between TAC, MTX, and LEF, however, the association between LEF use and the risk of ILD progression was significant in subgroups with poor lung function.

Summary:

We included five low-quality observational studies (Li, L. et al., 2022,[1] Tsuji et al., 2020,[2] Hozumi et al., 2019,[3] and Kurita et al., 2015[4], and Kim et al., 2022[5]) that addressed this particular PICO question. No randomized controlled trials addressed this question.

Results from RCTs:

None reported.

Results from observational studies:

The five observational studies included here describe the use of tacrolimus as first-line treatment for new-onset IIM-ILD but always as part of a multimodal treatment approach (i.e., no studies describe the use of tacrolimus monotherapy to treat IIM-ILD) (Table 30-1). For example, Li L et al., 2022[1] recently presented a study comparing the following two complex regimens: (1) prednisolone, tacrolimus, and pulse-dose methylprednisolone and/or CYC for a present-day cohort; and (2) prednisolone, pulse-dose methylprednisolone, and IV CsA and/or CYC for a historical control cohort.[1] Other studies similarly present clinical outcomes using treatment regimens that include tacrolimus but also other agents such as high-dose steroids and CYC. The "cleanest" study was a retrospective cohort study of 32 patients with DM/PM-ILD comparing prednisolone alone versus prednisolone in combination with a

calcineurin inhibitor (CNI). In this study, patients receiving CNI therapy in addition to prednisolone had improved progression-free survival and lower rates of disease recurrence compared to those only receiving prednisolone.[3] While this study and one other study suggest tacrolimus in combination with glucocorticoids can be an effective treatment regimen in newly diagnosed IIM-ILD, their observational study designs and limited sample sizes preclude the ability to recommend tacrolimus as first-line therapy strongly.

Lastly, one study[5] comparing the association of drug use on ILD progression showed insignificant differences between TAC, MTX, and LEF, however, the association between LEF use and the risk of ILD progression was significant in subgroups with poor lung function (aHR, 8.42; 95% CI, 2.61, 27.15).

Table 30-1: **Summary of clinical outcomes data in observational studies**

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Li et al. 2022[1]	Retrospective cohort study	High	Patients observed for 30 months regardless of the effects of the outcome After 30 months, PFT values were compared to baseline In addition, end-of-treatment PFT values compared between two treatment groups	60 patients with DM-ILD accordingly to EULAR/ACR criteria	24 patients treated with IV prednisolone 1-2 mg/kg/day + tac (goal 5-20 ng/ml) + methylpred 1 gm x 3 days and/or CYC 500 mg/m^2/month (TI group) vs. 36 patients (historical control) treated with prednisolone 1-2 mg/kg/day + methylpred 1 gm x 3 days and/or IV CsA 2-3 mg/kg/day and/or CYC 500 mg/m^2/month (CT group)	FVC % predicted values (before vs. 30 months after treatment): TI: 79.6 (9.2), 85.4 (5.8) CT: 81.5 (6.3), 86.0 (3.3) *p*=0.80 (represents comparison of values for TI vs. CT after 30 months of treatment) DLCO % predicted values (before vs 30 months after treatment): TI: 48.2 (8.4), 54.0 (5.6) CT: 52.2 (7.2), 57.7 (4.5) *p*<0.001 TLC (L) values (before vs 30 months after treatment) TI: 4.2 (0.3), 4.3 (0.2) CT: 4.2 (0.3), 4.3 (0.2) *P*=0.64 **Adverse events summarized in Table 30-2**

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Tsuji et al. 2020[2]	Prospective cohort study	High	Primary endpoint: 6-month survival rate Secondary endpoint: 12-month survival rate, adverse events, changes in lab data	Adult Japanese patients with new-onset MDA-5-positive DM-ILD (*n*=29) treated with combined high-dose GCs, tac, IV CYC, and possible PLEX vs. historical controls (*n*=15) who received "step-up" treatment (high-dose GCs and stepwise addition of immunosuppressant) Additional historical control group who received combined high-dose GCs, CsA, IV CYC also compared to more recent prospective cohort	Prednisolone 1 mg/kg/day (4 weeks), then gradually reduced+IV CYC (500-1,000 mg/m^2 every 2 weeks for 6 doses, then every 4-8 weeks for total 10-15 infusions)+tac (goal trough 10-12 ng/ml); PLEX could be initiated if condition worsened (performed 1-3 times per week for 3-13 consecutive weeks)	Combined IS group had higher 6-month mortality (89% vs. 33%, $p<0.0001$) Improvements in anti-MDA-5 titers, serum ferritin levels, FVC and HRCT scores also noted over 52-week period **Adverse events summarized in Table 30-3** PLEX initiation occurred in 31% of combined IS group and 7% of step-up group (NS)
Hozumi et al. 2019[3]	Retrospective cohort study	High	Progression-free survival rate, defined as time from date of initiation of first-line therapy until the date of first disease progression of PM/DM-ILD, death, or most recent visit;	32 patients with DM/PM-ILD and positive for an anti-ARS antibodies 12 treated with prednisolone (PSL) alone vs. 20 treated with PSL+CNI (4 on tac, 16 on CsA) Inclusion criteria: 2 years of follow-up or died within 2 years	PSL vs. PSL+CNI (tac or CsA)	No patients discontinued first-line therapy because of treatment-related adverse events 2-year PFS rate: 85% in PSL+CNI vs. 41.2% in PSL group, $p=0.02$ Cumulative 5-year survival rates: 91.7% in PSL+CNI vs. 100% in PSL, $p=0.92$ First-line therapy with PSL alone vs. PSL+CNI associated with worse progression-free survival (HR 2.88, $p=0.04$ on univariate analysis; HR

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
			disease progression defined as "deterioration of PM/DM-ILD"	Propensity score matching utilized to compare PSL+CNI (*n*=12) vs. PSL (*n*=12)		7.29, *p*=0.001 on multivariate analysis Propensity score matching results: 2-year PFS rate: 91.7% in PSL+CNI vs. 41.7% in PSL, *p*=0.03 Recurrence rate: 8.3% in PSL+CNI vs. 33.3% in PSL, *p*=0.04 No difference in cumulative survival rate **Adverse events summarized in Table 30-2**
Kurita et al. 2015[4]	Retrospective cohort study	High	Time to relapse or death of respiratory cause or serious adverse event	Patients with PM/DM-ILD Patients divided based on whether tx regimen included tac (started within 28 days of start of treatment) Exclusion criteria: Inclusion body myositis, malignancy-associated or overlapping cases	All patients treated with PSL 0.8-1 mg/kg/day IV pulse-dose methylpred (1 gm x 3 days) and/or another IS agent such as CsA (2-3 mg/kg/day), CYC (500 mg/m^2 monthly), or tac given as discretion of treating physician Tac starting dose: 1-3 mg/day; adjusted to target levels 5-20 ng/ml	Tac vs. no tac comparisons: Relapse rate: 20.8% vs. 20.0% Death due to respiratory cause: 4.2% vs. 20.0% Other SAE: 4.2% vs. 8.0% No differences between groups regarding change in FVC or DLCO (data not shown) Tac group had significant longer event-free survival (weighted HR 0.32, *p*=0.008) and disease-free survival (weighted HR 0.25, *p*=.005) **Adverse events summarized in Table 30-2**
Kim 2022[5]	Cross-sectional study	High	33 months	143 patients with RA-associated ILD	Glucocorticoids, MTX, LEF, tacrolimus, and biological or targeted synthetic DMARDs as confounding factors in the analysis. 61	64 patients experienced ILD progression during a median follow-up period of 33months. The use of MTX [adjusted hazard ratio (aHR), 1.06; 95% CI, 0.59, 1.89], LEF (aHR, 1.75; 95% CI, 0.88, 3.46) and

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
					(42.7%), 26 (18.2%) and 56 (39.2%) patients were exposed to MTX, LEF and tacrolimus during the follow-up period, respectively.	tacrolimus (aHR, 0.94; 95% CI, 0.52, 1.72) did not increase the risk of ILD progression. However, the association between LEF use and the risk of ILD progression was significant in subgroups with poor lung function (aHR, 8.42; 95% CI, 2.61, 27.15). Number of patients with RA-associated ILD progression /population: **TAC use**: No 42/87 (48.3%), Yes 22/56 (39.3%), Unadjusted HR (95% CI) 0.66 (0.39, 1.12), Adjusted HR (95% CI) 0.94 (0.52, 1.72). **MTX use**: No 37/82 (45.1%), Yes 27/61 (44.3%), Unadjusted HR (95% CI) 0.84 (0.51, 1.39), Adjusted HR (95% CI) 1.06 (0.59, 1.89); **LEF use**: No 48/117 (41.0%), Yes 16/26 (61.5%), Unadjusted HR (95% CI) 1.86 (1.05, 3.28), Adjusted HR (95% CI) 1.75 (0.88, 3.46);

Table 30-2: Summary of adverse events found in observational studies comparing tacrolimus to no tacrolimus for first line ILD therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tacrolimus	no tacrolimus	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events in observational studies												
3 Li, L. et al., 2022[1], Hozumi et al., 2019[3], Kurita et al., 2015[4]	observational studies	serious[a]	not serious	serious[b]	serious[c]		30/195 (15.4%)	50/240 (20.8%)	**RR 0.83** (0.47 to 1.48)	**35 fewer per 1,000** (from 110 fewer to 100 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Relapse												
2 Li, L. et al., 2022[1], Kurita et al., 2015[4])	observational studies	serious[a]	not serious	serious[b]	serious[c]		16/49 (32.7%)	19/60 (31.7%)	**RR 1.13** (0.67 to 1.90)	**41 more per 1,000** (from 104 fewer to 285 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Death												
3 Li, L. et al., 2022[1], Hozumi et al., 2019[3], Kurita et al., 2015[4]	observational studies	serious[a]	not serious	serious[b]	not serious		4/61 (6.6%)	20/72 (27.8%)	**RR 0.29** (0.11 to 0.75)	**197 fewer per 1,000** (from 247 fewer to 69 fewer)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Hepatic cirrhosis												
1 Li, L. et al., 2022[1]	observational studies	serious[a]	not serious	serious[b]	serious[d]		2/24 (8.3%)	0/36 (0.0%)	**RR 7.40** (0.37 to 147.69)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Malignancies (any)												
1 Li, L. et al., 2022[1]	observational studies	serious[a]	not serious	serious[b]	serious[c, d]		0/24 (0.0%)	6/36 (16.7%)	**RR 0.11** (0.01 to 1.93)	**148 fewer per 1,000** (from 165 fewer to 155 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Any adverse events												
2 Hozumi et al., 2019[3], Kurita et al., 2015[4]	observational studies	serious[a]	not serious	serious[b]	serious[c]		8/37 (21.6%)	5/36 (13.9%)	**RR 1.59** (0.60 to 4.20)	**82 more per 1,000** (from 56 fewer to 444 more)	⨁◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

a. retrospective cohort study
b. Indirect comparison

c. 95% CI includes the line of no difference
d. Very few events

Table 30-3: Summary of adverse events found in observational studies comparing tacrolimus+prednisolone+IV CYC to steroid+"step-up" IS for first-line ILD therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tacrolimus+prednisolone+IV CYC	steroid+"step-up" IS	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events in observational studies												
Tsuji et al., 2020[2]	observational studies	serious[a]	not serious	serious[b]	serious[c]		29/81 (35.8%)	12/45 (26.7%)	**RR 1.09** (0.81 to 1.47)	**24 more per 1,000** (from 51 fewer to 125 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Infection (any)												
Tsuji et al., 2020[2]	observational studies	serious[a]	not serious	serious[b]	serious[c]		23/27 (85.2%)	12/15 (80.0%)	**RR 1.06** (0.79 to 1.43)	**48 more per 1,000** (from 168 fewer to 344 more)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - Hemorrhagic cystitis												
Tsuji et al., 2020[2]	observational studies	serious[a]	not serious	serious[b]	serious[d]		4/27 (14.8%)	0/15 (0.0%)	**RR 5.14** (0.30 to 89.48)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	Critical
Serious adverse events in observational studies - TMA												
Tsuji et al., 2020[2]	observational studies	serious[a]	not serious	serious[b]	serious[d]		2/27 (7.4%)	0/15 (0.0%)	**RR 2.86** (0.15 to 55.89)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

a. Prospective cohort study retrospective cohort study
b. Indirect comparison
c. 95% CI includes the line of no difference
d. Very few events

Table 30-4. PICO 30 Excluded Studies

References	Reasons for Exclusion
Takada et al. 2020[6]	Not a comparator of interest
Okamoto et al. 2016[7]	No intervention of interest
Wilkes et al. 2005[8]	Not a comparator of interest

References

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PICO 31: In rheumatic disease patients with ILD, what is the impact of anti-TNF therapy compared to no anti-TNF therapy as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Four observational studies were included, one of which only provided data on infectious complications. None of these studies provide direct evidence that specifically addresses whether anti-TNF therapy is beneficial compared to no anti-TNF therapy as a first-line treatment for CTD-ILD.

Summary:

We included four low-quality observational studies (Chen et al., 2022,[1] Ma et al., 2017,[2] Zamora-Legoff et al., 2016,[3] and Dixon et al., 2010[4]) that addressed this particular PICO question. There were no randomized controlled trials addressing this PICO question.

Results from RCTs:

None reported.

Results from observational studies:

The four observational studies included here describing the use of anti-TNF therapies in treating CTD-ILD only indirectly address PICO 31. Perhaps the best (albeit still very limited) evidence comes from a 2010 retrospective cohort study by Dixon et al., 2010[4] in which 367 RA-ILD were treated with either any of the 3 anti-TNF therapies or with any conventional DMARD (within-cohort DMARD use percentages and mean or median doses are not specified). One could possibly infer that differences in respiratory-specific outcomes are related, at least in part, to anti-TNF therapies, although lack of clarity regarding conventional DMARD use in this study limit interpretation of these data specifically as it relates to PICO 31. Nonetheless, 68 deaths/1,000 person-years were noted in the anti-TNF group and 92 deaths/1,000 person-years in the DMARD group, with age- and sex-adjusted mortality rate ratio of 1.26 (95% 0.69-2.31). RA-ILD was reported as the specific cause of death in 15 out of 70 patients (21%) in the anti-TNF group and 1 out of 14 patients (7%) in the csDMARD group. Another study simply looked across several clinical covariates to determine which were associated with progressive RA-ILD and reported an HR for being prescribed anti-TNF therapies of 0.44 (95% CI 0.17-1.15, p=0.08), suggesting a trend towards possible benefit (recognizing that the comparator group was patients that could be on any other treatments except anti-TNF therapies).[1] Lastly, a small prospective cohort study demonstrated better PFT parameters among patients on

infliximab in combination with prednisone as compared to patients on a multimodal treatment regimen consisting of prednisone and either cyclosporine A, CYC, or azathioprine.[2] These data are merely hypothesis-generating and do not concretely tell us whether there is a benefit in using anti-TNF therapies versus no anti-TNF therapies in treating CTD-ILD.

Table 31-1: PICO 31: anti-TNF therapy compared to no anti-TNF therapy; summary of clinical outcomes data in observational studies

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Chen et al. 2022[1]	Retrospective cohort study	High	Pulmonary functional impairment compared with the diagnosis of baseline time, assessed by changes of HRCT score or PFT during follow-up	RA-ILD patients seen at Changhai Hospital, divided into the "progressive group" (*n*=32) and the "stable group" (*n*=43)	Univariate Cox survival analyses performed to determine whether certain demographic covariates, lab data, PFT data, or CT pattern associated with "progressive" disease	Association of TNF inhibitors with RA-ILD progression: unadjusted HR 0.44 (95% CI 0.17-1.15, *p*=0.08)
Ma et al. 2017[2]	Prospective cohort study	High	Treatment regimens lasted for 16-24 weeks in both groups Outcomes reported at baseline, on hospital discharge, 6 months, and 12 months	40 PM/DM-ILD patients admitted and initiated on tx with two regimens based on patient preference: conventional (steroids in combo with IS agents) (*n*=20) vs. infliximab group (steroids plus infliximab) (*n*=14) 4 patients dropped out; 2 patients lost to follow-up	Prednisone 0.5-2 mg/kg daily x 1 mo, then tapered+CsA 150-200 mg/day or CYC 0.8-1.2 g/month or AZA 75-150 mg/day vs. prednisone 0.5-2 mg/kg daily+infliximab 5 gm/kg given at 0, 2, 6, and 14 weeks, then bimonthly	ITT analysis NOT performed 14 patients in infliximab group and 20 patients on conventional group No differences in myositis Abs On discharge, levels of PaO_2 and $PaCO_2$ and muscle strength better in infliximab group ($p<0.05$) At 6 months, FEV1, FVC, and DLCO better in infliximab group ($p<0.05$) No differences in any adverse events (21.4% in infliximab vs. 40.0% in convention, *p*=0.26)

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						One-year survival: 85.7% in infliximab group vs. 65.0% in convention group, *p*=0.162 **Adverse events summarized in Table 31-2**
Zamora-Legoff et al. 2016[3]	Retrospective cohort study	High	Risk of infection analyzed by person-year methods using time-dependent covariates started when med first used up until 30 days after stopping	RA-ILD patients seen at Mayo Clinic Exclusion criteria: patients with concomitant rheumatological disease (except for secondary SS)	48 patients on no therapy 59 patients on TNFi (alone or in combo with any other antirheumatic drug)	Infection rates: 1.8 per 100 PY in TNFi group vs. 6.6 per 100 PY in no therapy group
Dixon et al. 2010[4]	Retrospective cohort study	High	Per outcomes	367 patients with preexisting RA-ILD from British Society for Rheumatology Biologics Register: 299 treated with anti-TNF and 68 treated with DMARDs	Anti-TNF vs. DMARD (doses and specific DMARDs not specified)	70/299 patients (23%) in anti-TNF cohort died after median follow-up 3.8 years vs. 14/68 patients (21%) in DMARD cohort after median follow-up 2.1 years 68 deaths/1000 person-years in anti-TNF vs. 92 deaths/1000 person-years in DMARD group à age- and sex-adjusted mortality rate ratio 1.26 (95% CI 0.69-2.31); fully adjusted MRR 0.81 (95% CI 0.38-1.73) RA-ILD as cause of death: 15/70 (21%) patients for anti-TNF group 1/14 (7%) patients for DMARD group

Table 31-2: PICO 31: anti-TNF therapy compared to no anti-TNF therapy; summary of adverse events found in observational studies comparing prednisone+anti-TNF to prednisone+other IS (CsA, AZA, or CYC) for first-line ILD therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone+anti-TNF	prednisone+other IS (CsA, AZA, or CYC)	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events in observational studies - Death (any cause)												
Ma, J. et al., 2017[2]	observational studies	serious [a]	not serious	not serious	very serious [b,c,d]		2/14 (14.3%)	7/20 (35.0%)	**RR 0.41** (0.10 to 1.68)	**207 fewer per 1,000** (from 315 fewer to 238 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in observational studies - Death due to respiratory failure												
Ma, J. et al., 2017[2]	observational studies	serious [a]	not serious	not serious	very serious [b,c,d]		2/14 (14.3%)	5/20 (25.0%)	**RR 0.57** (0.13 to 2.54)	**108 fewer per 1,000** (from 218 fewer to 385 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in observational studies - Death due to pulmonary infection												
Ma, J. et al., 2017[2]	observational studies	serious [a]	not serious	not serious	very serious [b,c,d]		0/14 (0.0%)	2/20 (10.0%)	**RR 0.28** (0.01 to 5.42)	**72 fewer per 1,000** (from 99 fewer to 442 more)	⊕◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

- **a.** no randomization or blinding
- **b.** single study, <50 patients
- **c.** very few events
- **d.** 95% CI includes the line of no difference, wide CIs

Table 31-3: PICO 31 Excluded Studies

Reference	Reason for exclusion
Kang et al. 2020[5]	Not a comparator of interest

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PICO 32: In rheumatic disease patients with ILD, what is the impact of abatacept compared to no abatacept as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- One retrospective study without a comparator group evaluated 16 RA-ILD patients who received abatacept for at least one year. No patients had a worsening in ILD severity during the study period.[1]
- In one small retrospective study that included 44 patients who received abatacept and 31 patients who received a JAKi, there was no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.[2]
- Although the differences were small, one retrospective study of RA-ILD patients demonstrated that receiving abatacept vs any form of TNFi may be associated with a decreased risk of ILD exacerbation or serious respiratory complications.[3]

Summary:

Three observational studies indirectly address this PICO question.

In a small observational study by Nakashita et al. 2016,[1] 16 RA-ILD patients who received abatacept for at least one year were retrospectively analyzed without a relevant comparison group. CT severity scores were calculated. No patients had a worsening CT score at the end of one year, and two patients with the lowest score had resolution of their lung disease.

In a study by Tardella et al. 2022,[2] 31 RA-ILD patients who received a JAKi and 44 patients who received abatacept were retrospectively studied using a computer-aided method (CaM) to assess changes in (HRCT) fibrosis percentage. Patients were classified as worsened (15% more fibrosis), stable, or improved (15% less fibrosis). After 18 months, 5 (11.4%) patients showed a HRCT deterioration, 32 (72.6%) were considered stable, and 7 (16.0%) patients showed an HRCT improvement in the ABA group. In the JAKis group 5 (16.1%) patients showed an HRCT deterioration, 20 (64.5%) were considered stable, and 6 (19.4%) patients showed an HRCT improvement. There was no significant change in mean FVC, DLCO, or CT fibrosis scores. Abatacept was not first-line treatment for this study and patients concomitantly taking methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs) and/or glucocorticoids at a dose of less than 10 mg daily prednisone or equivalent were included.

In a study by Kang et al. 2020[3] RA-ILD patients who received treatment with abatacept or a TNFi were identified from U.S. Medicare and Truven MarketScan databases. The primary outcome was in-patient or ED exacerbation of the underlying primary pulmonary comorbidity based on ED visit or hospitalization. 1999 RA-ILD patients met initial inclusion criteria; 1579 received a TNFi and 420 received abatacept. The mean follow-up time for the abatacept group ranged between 1.0- 1.6 years for different

databases and outcomes, and the range was 1.4-1.6 years for the TNFi group. The IRR of ILD exacerbation associated with abatacept was 0.68 (95%CI 0.54-0.87) in Medicare and 0.27 (95%CI 0.16-0.47) in MarketScan with a combined IRR of 0.44 (95%CI 0.18-1.09, p for heterogeneity=0.003). The IRR for serious respiratory complications was 0.71 (0.59, 0.86). This study does not directly address the question of abatacept vs no abatacept. Furthermore, a significant proportion of patients in each group had received therapy with concurrent immunosuppression, including steroids, MTX, and Leflunomide.

Table 32-1: Impact of abatacept vs no abatacept as first line ILD treatment

Ref ID, Author, Year	Study	Risk of bias	Follow-up	Population Description	Treatment and Comparator	Results
Kang et al. 2020[3]	Retrospective cohort study	High		1999 RA-ILD patients who had received either TNFi or abatacept	1579 who received TNFi, 420 who received abatacept Outcome was composite inpatient or ED admission for ILD exacerbation	Mean follow-up time: ABA ranged from 1.0-1.6 years for different databases; ranged from 1.4-1.6 years for the TNFi group. The IRR of ILD exacerbation associated with abatacept was 0.68 (95%CI 0.54-0.87) in Medicare and 0.27 (95%CI 0.16-0.47) in MarketScan with a combined IRR of 0.44 (95%CI 0.18-1.09, p for heterogeneity=0.003). The IRR for serious respiratory complications was 0.71 (0.59, 0.86).
Tardella et al. 2022[2]	Retrospective observational study	High		75 RA-ILD patients who received either JAKis or abatacept. Seventy-five patients (69.3% women) were evaluated, 31 received a JAKi while 44 received ABA.	31 patients who received a JAKi and 44 patients who received Abatacept. Computer-aided method (CaM) used to assess changes in (HRCT) fibrosis percentage and classify patients as worsened (15% more), stable, or improved (15% less) fibrosis after 18 months.	Abatacept JAKis Time 0 Time 18 Time 0 Time 18 DLCO 58.69 61.36 59.72 62.77 FVC 82.29 81.24 81.18 79.59 HRCTcam 19.41 18.94 18.54 17.52 All p values NS CT deterioration Stability Improved ABA 5 (11.4%) 32 (72.6%) 7 (16%)

						JAKis 5 (16%) 20 (65.5%) 6 (19.4%)
Nakashita et al. 2016[1]	Retrospective observational study	High		RA-ILD patients who received abatacept for at least one year	16 RA-ILD patients ILD severity scores were graded from 1-3 based on CT findings.	After the initiation of abatacept, none of the patients experienced worsening of ILD severity at one year (p=0.157). 2 patients with grade 1 ILD showed complete resolution.

Table 32-2: PICO 32: Excluded Studies Table

Reference	Notes
Mena-Vazquez et al., 2022[4]	Wrong study design
Tardella et al., 2022[5]	Wrong study design
Fernandez-Diaz et al., 2021[6]	Wrong study design
Vicente-Rabaneda et al., 2021[7]	Wrong study design
Cassone et al., 2020[8]	Wrong study design

Note: The above studies: Fernandez-Diaz et al., 2021[6], Mena-Vazquez et al., 2022[4], and Vicente-Rabaneda et al., 2021[7] were considered as additional resources to provide evidence in support of the following statement in the manuscript: 'Studies suggest no worsening of ILD with abatacept(75,81-83), thus discontinuation because of ILD is not necessary; efficacy of abatacept for ILD is uncertain.'

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PICO 33: In rheumatic disease patients with ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to no anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Summary:

We included one non-blinded randomized controlled proof-of-principle study (Daoussis et al., 2010[1]) and five low-quality observational studies (Amlani et al., 2020,[2] Korsten et al., 2020,[3] Daoussis et al., 2017,[4] Jordan et al., 2015[5], and Matson et al., 2022[6]) that addressed this PICO question.

Results from RCTs:

A single non-blinded, non-placebo-controlled proof-of-principle randomized study described the benefit of receiving rituximab versus no rituximab but only in SSc-ILD patients already on "standard treatment," which could have consisted of any number of medications as long as they were not started, stopped, or dose-adjusted in the preceding 12 months. In this study, the addition of rituximab led to improvements in both FVC and DLCO % predicted, while no improvements were noted in the control group (Table 33-1).[1] The non-

blinded nature of this study and its extremely limited sample size (14 patients in total) limit the quality of evidence. Though rituximab may be beneficial as a first-line treatment for CTD-ILD, larger studies are needed.

Results from observational studies:

Only three observational studies provided low-quality evidence addressing PICO 33, with findings summarized in Table 2. Notably, one pSS-ILD study included only 6 patients on rituximab and 5 patients receiving no treatment with no differences noted in FVC and DLCO % predicted slope changes before and after initiation of treatment.[2] Another retrospective cohort study examined 12 patients with ASyS-ILD who had either received rituximab or never received rituximab.[3] Among the 7 patients who received rituximab, only 2 started it at the time of ILD diagnosis. In this study, no major radiographic differences were noted on serial CTs between the two study arms, nor were PFT differences noted. A multicenter open-label trial comparing RTX to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of RTX in treating SSc-ILD based on standard PFT metrics (FVC and DLCO % predicted).[4] However, a significant number of patients in the RTX arm were receiving concomitant DMARDs (*n*=13, 39.4%) and/or steroids (*n*=18, 54.5%), and a significant number of patients in the conventional arm were receiving concomitant steroids (*n*=17, 94.4%). The open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data. Lastly, in a nested case-control study, rituximab was shown to significantly prevent further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients (9 in each arm).[5] Taken together, these data support a possible role for rituximab in treating CTD-ILD, particularly SSc-ILD; however, recommendations on exact dosing regimens and the ideal timing of treatment initiation (first-line versus add-on therapy for disease progression) cannot be made based on existing literature. Lastly, one study[6] showed that among patients taking AZA, MMF, and RTX, FVC% predicted was highest for MMF (4.55%), then AZA (3.84%) and RTX (3.26%), while DLCO% predicted was highest for RTX (6.73%), then MMF (3.67%) and AZA (1.93%). The adverse events were highest in AZA (19.6%), then MMF (15.6%) and RTX (11.6%).

Table 33-1: PICO 33: impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to no anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first-line ILD treatment; summary of clinical outcomes data in randomized controlled trials

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Daoussis et al. 2010[1]	Non-blinded, non-placebo-controlled proof-of-principle randomized study	High	Patients with SSc-ILD Inclusion criteria: anti-Scl-70-positive; ILD based on HRCT, PFTs, or both; no medication or dose changes 12 months prior to enrollment Patients randomized according to odd vs. even birthdays	8 patients assigned to RTX group; 6 patients assigned to control group	RTX group received four weekly pulses of RTX 375 mg/m^2 at baseline and at 6 months on top of already administered IS	FVC data: RTX group: 68.13 (SD 19.69) at baseline vs. 75.63 (SD 19.73) at 1 year, p=0.0018 Control group: 86 (SD 19.57) at baseline vs. 81.67 (SD 20.69) at 1 year, p=0.23 Median FVC percent changes: 10.25% (6.19-18.65) in RTX group vs. -5.04% (4.11-11.6) in control group, p=0.002 DLCO data: RTX group: 52.25 (SD 20.71) at baseline vs 62 (23.21) at 1 year, p=0.017 Control group: 65.33 (SD 21.43) at baseline vs. 60.17 (SD 23.69) at 1 year, p=0.25 Median DLCO changes: 19.46% (3.7-30.8) in RTX group vs. -7.5% (1.4-26.57), p=0.023 mRSS scores: RTX group: 13.5 (SD 6.84) at baseline vs. 8.37 (SD 6.45) at 1 year, p=0.0003 Control group: 11.50 (SD 2.16) at baseline vs. 9.66 (SD 3.38) at 1 year, p=0.16 Median mRSS score changes: 39.25% (27.33-64.95) in RTX group compared with 20.80% (10.78-39.28), p=0.06 1 patient in RTX group suffered a respiratory tract infection requiring hospitalization; no other adverse events reported

Table 33-2: PICO 33: impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to no anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first-line ILD treatment; summary of clinical outcomes data in observational studies

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Amlani et al. 2020[2]	Retrospective cohort study	High	Slope in FVC and DLCO % predicted were plotted 12 months before and 12 months after treatment initiation	19 patients with pSS-associated ILD; AZA group (*n*=7): 86% female, mean age 57.7; MMF group (*n*=7): 71% female, mean age 58.9; RTX group (*n*=6): 83% female, mean age 55.7; no treatment group (*n*=5): 100% female, mean age 69.6 Inclusion criteria: ≥18 years old with pSS diagnosis and had clinically confirmed ILD Exclusion criteria: Another autoimmune disease present	AZA vs. MMF vs. RTX vs. no treatment (doses not specified)	Compared pre- and post-treatment slopes for FVC and DLCO % predicted determined by linear effects models. NOTE: 5/6 patients treated with RTX had received or were receiving MMF or AZA and only 3/6 had PFT data available before and after treatment. FVC % predicted slope change before RTX: 9% per month; slope change after RTX: 3% per month; *p*=0.18. DLCO % predicted slope change before RTX: 5% per month; slope change after RTX: -2% per month; *p*=0.43. Adverse events for RTX not reported.

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Korsten et al. 2020[3]	Retrospective cohort study	High	Medium follow-up time was 31 (6-156 months); HRCT scores and PFTs assessed "before and during" treatment, using the first and "any subsequent" testing; HRCT scores 0-4 (0=absence; 4=76-100% involvement)	12 patients with ASyS-associated ILD seen at the University Medical Center Goettingen who received (*n*=7) or never (*n*=5) received RTX; among RTX patients, 4/7 started RTX because of ILD progression, 2/7 at time of ILD diagnosis, 1/7 for treatment of concomitant anti-CCP-positive RA; all patients also on other IS agents	Ever RTX vs. never RTX (doses not specified)	No differences in CT scores for CT 1, CT 2, or CT 3 (time intervals vary) were reported. Additionally, no difference in presence of GGOs, lung fibrosis/interlobular changes and bronchiectasis, and honeycombing were reported. Lastly, no difference in FVC % predicted and DLCO % predicted in RTX and no RTX groups before and after initiation of treatment were noted.
Dauossis et al. 2017[4]	Multicenter open-label trial	High	Median follow-up was 7 years but ranged 1-7 years with significant loss to follow-up	51 patients with SSc-ILD who received either RTX (*n*=33) or conventional treatment consisting of AZA, MMF, or MTX (*n*=18) Of note, RTX arm could receive concurrent IS therapies (MTX=2, HCQ=1, MMF=10, steroids=33); conventional arm could receive concurrent steroids (n=17)	RTX arm received 2 or more cycles with each cycle consisting of four infusions at dose of 375 mg/m^2 weekly; cycles repeated every 6 months Doses in conventional	FVC % predicted comparisons: RTX arm showed increase in FVC % predicted at 2 years (80.6±21.2 at baseline vs. 86.9±20.6 at 2 years, *p*=0.041), whereas conventional group showed no change (77.7±18.3 at baseline vs. 77.6±19.5 at 2 years, *p*=NS) Trend towards improved FVC % predicted in RTX vs.

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
				Also of note, 7 patients in RTX arm had received CYC in past but not within 1 year prior to trial enrollment RTX arm had longer disease duration prior to enrollment (5.7 vs. 2.6 years, *p*=0.01) but baseline characteristics otherwise comparable	arm not specified	conventional group at 2 years (*p*=0.06) Higher FVC % predicted in RTX group (*n*=5) vs. conventional group (*n*=9) at 7 years (91.6±14.8 vs. 61.1±15.7, *p*<0.01), noting significant loss to follow-up DLCO % predicted comparisons: Trend towards improvement in DLCO % predicted in RTX arm at 2 years (59.2±18.2 vs. 61.6±17.6, *p*=0.053), whereas no change noted in conventional group (64.2±25.5 vs. 63.1±24.0, *p*=0.38) No difference between RTX and conventional arms when directly comparing DLCO % predicted at 2-year mark (*p*=0.97) and at 7-year mark (*p*=0.50) Linear mixed model analysis account for disease duration,

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						baseline PFTs, baseline mRSS showed RTX associated with improvement in FVC (p=0.004) and DLCO (p=0.04) compared to control group
Jordan et al. 2015[5]	Nested case-control study	High	Primary outcome: mRSS change from baseline; secondary outcome: change in FVC from baseline; patients followed for 6+ months	Subgroup analysis of 50 patients with diffuse, severe SSc enrolled in EUSTAR database, some of which had ILD; RTX-treated patients matched with control patients not treated with RTX Matching parameters for mRSS analysis: baseline mRSS, follow-up duration, scleroderma subtype, disease duration, IS co-treatment Matching parameters for ILD analysis: baseline FVC, follow-up duration, disease duration, and IS co-treatment	In RTX group, most frequent application was 2 infusions of 1000 mg in 2 weeks (75% of patients) but other regimens were also included.	50 patients included in mRSS analysis (25 in each group); mRSS % changes were larger in the RTX group versus matched controls (-24.0±5.2% vs -7.7±4.3%, p=0.03). Among 18 SSc-ILD patients (9 in each group), RTX prevented a significantly further decline of FVC compared with matched controls (0.4±4.4% vs -7.7±3.6%, p=0.02). No serious adverse events reported in RTX group (data on adverse events for non-RTX group not provided for comparison).

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Matson 2022[6]	Retrospective cohort study	High	The median follow-up time was 27.5 months	212 patients diagnosed with RA-ILD	Initial treatments with Azathioprine vs. Mycophenolate vs. Rituximab	FVC % predicted at 12 months: Azathioprine 3.84%; Mycophenolate 4.55%; Rituximab 3.26% DLCO % predicted at 12 months: Azathioprine 1.93%; Mycophenolate 3.67%; Rituximab 6.73% **Adverse events:** All AE: : Azathioprine 18 (19.6%); Mycophenolate 12 (15.6%); Rituximab 5 (11.6%) GI upset: Azathioprine 3 (3.3%); Mycophenolate 5 (6.5%); Rituximab 1 (2.3%) Elevated liver enzymes: Azathioprine 3 (3.3%); Mycophenolate 0 %; Rituximab 0 Cytopenia: Azathioprine 3 (3.3%); Mycophenolate 2 (2.6%); Rituximab 1 (2.3%)

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						Recurrent infections: Azathioprine 4 (4.3%); Mycophenolate 2 (2.6%); Rituximab 1 (2.3%) Non-specific symptoms: Azathioprine 5 (5.4%); Mycophenolate 3 (3.9%); Rituximab 2 (4.7%) Treatment stopped due to adverse event: Azathioprine 12 (13.0%); Mycophenolate 3 (3.9%); Rituximab 1 (2.3%).

Table 33-3. PICO 33 Excluded Studies

Reference	Reason for exclusion
Jensen et al. 2019[7]	Wrong study design
Daoussis et al. 2012[8]	Wrong study design
Yusof et al. 2017[9]	Not a comparator of interest
Jordan et al. 2014[10]	Duplicate reference
Kelly et al. 2021[11]	Not a population of interest
Langlois et al. 2020[12]	Does not address PICO

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Table 33-4: Additional resources to consider

Reference	Notes
Maher et al. 2023[13]	January 8th comment from Michael George suggesting adding Maher 2023 (later identified in bridge search). https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00359-9/fulltext.

PICO 34: In rheumatic disease patients with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first-line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.
- The above study's preceding phase 2 randomized controlled trial demonstrated slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a post hoc analysis of the RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.
- One observational study of SSc patients reported no difference for FVC% predicted with tocilizumab vs without tocilizumab at 12 months.

Summary:

We included two multicenter, randomized, double-blind, placebo-controlled trial (Khanna et al., 2020[1] and Khanna et al. 2016[2]), one post hoc analysis of Khanna 2020 (Roofeh et al., 2021[3]), and one observational study (Kuster et al., 2022[4]) that addressed this PICO question.

Results from RCTs:

Two multicenter, randomized, double-blind, placebo-controlled trials were found that addressed PICO 34 (one phase 3 study and its phase 2 counterpart).[1] The phase 3 study included 210 patients with diffuse cutaneous SSc with or without ILD (mean age 48.2, 81% female, median disease duration <2 years [from the first non-Raynaud phenomenon manifestation]). Patients with an FVC <55%

predicted or with a DLCO <45% predicted were excluded (as not to include subjects with more advanced ILD). In addition, participants had to have elevated acute-phase reactant levels (at least one of the following: CRP >6 mg/L, ESR >28 mm/h, or platelet count >330 x 10^9/L). Subjects were randomized 1:1 to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo for 48 weeks, followed by a 48-week open-label period of tocilizumab. Of note, immunomodulatory therapy could be added to the study medication from week 16 onward for participants who had a decline in FVC % predicted or from week 24 onward for those who had worsening skin thickening or other SSc complications. mRSS and FVC were assessed at baseline and at weeks 8, 16, 24, 36, and 48. The primary outcome was the difference in change from baseline in mRSS at week 48 (presented as the difference in the least squares means), although several other secondary outcomes addressed more respiratory-focused and patient-centered metrics, such as differences in the distribution of change from baseline to week 48 in FVC % predicted (also presented as the difference in the least squares means) and differences from baseline to week 48 in HAQ-DI, SHAQ, SGRQ, and FACIT-fatigue scores. Results presented in Table 34-1 highlight the beneficial effects of tocilizumab on preserving lung function according to FVC measurements. This was demonstrated for the cohort at large but also in a subgroup analysis of patients with known SSc-ILD at baseline (*n*=136 patients with 68 patients in each study arm). Paired with more patient-centered outcomes such as improved St. George's Respiratory Questionnaire scores, this study (which was analyzed as intention-to-treat) suggests tocilizumab may be a useful first-line therapy in SSc patients with early ILD. The post hoc analysis described below more directly addresses PICO 34 in that it looked at the benefits of tocilizumab exclusively among patients with already established ILD.[3]

The phase 2 study enrolled 87 patients (43 assigned to tocilizumab and 44 assigned to placebo) and looked at least squares mean change in mRSS at 24 weeks as a primary endpoint.[2] It also included multiple secondary endpoints such as several patient- and physician-reported outcomes to 24 weeks and 48 weeks (e.g., HAQ-DI, patient global visual analog scale [VAS], FACIT-fatigue scores, and others) and change in mRSS from baseline to 48 weeks, among others. As exploratory endpoints, the study also reported change from baseline at 24 and 48 weeks in FVC (mL), FVC % predicted, and DLCO % predicted. In this study, tocilizumab 162 mg injections or placebo were administered weekly for 48 weeks. Similar to the phase 3 study, escape treatments with MTX, HCQ, or MMF were permitted after 24 weeks for patients with 20% or more worsening of their mRSS from baseline, worsening complications associated with SSc (e.g., arthritis), and/or new lung disease. In this study, tocilizumab was not statistically significantly associated with a significant reduction in skin thickening. However, the least squares mean difference in mRSS was greater in the tocilizumab group than in the placebo group (-3.92 vs. -1.22, *p*=0.09). In addition, tocilizumab was associated with a significantly smaller reduction in absolute FVC at 24 weeks compared to placebo (-34 mL vs. -171 mL, least squares mean difference 136 mL, *p*=0.04),

although this difference did not persist out to 48 weeks. In addition, fewer patients in the tocilizumab group than in the placebo group had worsening of FVC % predicted at 24 weeks (p=0.009) or at 48 weeks (p=0.037).

Results from observational studies:

One post hoc analysis of the RCT described above looked specifically at the benefits of using tocilizumab among patients with already established ILD, with results presented in Table 34-3.[2] Specifically, it included 136 SSc patients with ILD and found a slower decline in FVC % predicted among patients receiving tocilizumab versus placebo. Similarly, there was less radiographic progression in patients receiving tocilizumab. In addition to being a post hoc analysis, this study is limited by its use of surrogate outcomes (PFT metrics and CT findings). Lastly, Kuster et al. 2022[4] reported on 3273 patients with SSc treated with tocilizumab (n=93) vs standard of care (n=3180). At 12 months, no difference was reported for FVC% predicted with tocilizumab vs without tocilizumab.

Table 34-1: PICO 34: IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first-line ILD treatment; key findings from RCT comparing tocilizumab to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Toci	placebo	Relative (95% CI)	Absolute (95% CI)		
>10% decrease in FVC % predcited at 48 weeks												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	serious[a]	serious[b,c]	none	20/135 (14.8%)	28/136 (20.6%)	**RR 0.98** (0.24 to 4.00)	**4 fewer per 1,000** (from 156 fewer to 618 more)	⊕⊕◯◯ Low	Important
>10% decrease in FVC % predicted at 24 weeks												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	serious[a]	serious[b]	none	6/123 (4.9%)	22/127 (17.3%)	**RR 0.29** (0.12 to 0.70)	**123 fewer per 1,000** (from 152 fewer to 52 fewer)	⊕⊕◯◯ Low	Important
LSM change in FVC % predicted at 48 weeks												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	serious[a]	serious[b]	none	134	137	-	MD **4.16 higher** (3.79 higher to 4.53 higher)	⊕⊕◯◯ Low	Important
LSM change in FVC % predicted at 24 weeks												
1 Khanna 2016	randomised trials	not serious	not serious	serious[a]	serious[b]	none	35	36	-	MD **3.8 higher** (2.64 higher to 4.96 higher)	⊕⊕◯◯ Low	Important

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Toci	placebo	Relative (95% CI)	Absolute (95% CI)		
Change in observed HRCT QLF-WL at 48 weeks												
1 Khanna 2020	randomised trials	not serious	not serious	serious[a]	serious[b]	none	84	81	-	MD **0.8 lower** (0.94 lower to 0.66 lower)	⨁⨁◯◯ Low	Important
Change in observed HRCT QILD-WL at 48 weeks												
1 Khanna 2020	randomised trials	not serious	not serious	serious	serious[b]	none	84	80	-	MD **1.8 lower** (2.23 lower to 1.37 lower)	⨁⨁◯◯ Low	Important
Change in SGRQ at 48 weeks												
Khanna et al., 2020	randomised trials	not serious	not serious	not serious	serious[b]	none	104	106	-	MD **1.1 lower** (2.01 lower to 0.19 lower)	⨁⨁◯◯ Low	Critical
Change in HAQ-DI at 48 weeks												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	serious[b]	none	144	143	-	MD **0.12 lower** (0.27 lower to 0.03 higher)	⨁⨁◯◯ Low	Critical

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
a. Use of surrogate outcome
b. Small study; did not meet optimal information size; single study evidence base
c. Wide confidence intervals

Table 34-2: PICO 34: IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first-line ILD treatment; adverse events from RCT comparing tocilizumab to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Toci	placebo	Relative (95% CI)	Absolute (95% CI)		
Any adverse events in RCTs												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	serious[a, d]	none	113/147 (76.9%)	104/150 (69.3%)	**RR 1.11** (0.98 to 1.25)	**76 more per 1,000** (from 14 fewer to 173 more)	⊕⊕◯◯ Low	Critical
Serious adverse events in RCTs												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	serious[d]	none	63/545 (11.6%)	83/556 (14.9%)	**RR 0.77** (0.58 to 1.03)	**34 fewer per 1,000** (from 63 fewer to 4 more)	⊕⊕⊕◯ Moderate	Critical
Serious adverse events in RCTs - Death due to any cause												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	very serious[a,b,c,	none	4/147 (2.7%)	4/150 (2.7%)	**RR 1.03** (0.12 to 8.88)	**1 more per 1,000** (from 23 fewer to 210 more)	⊕◯◯◯ Very low	Critical
Serious adverse events in RCTs - Treatment failure												
1 Khanna 2020	randomised trials	not serious	not serious	not serious	Serious[a,b]	none	23/104 (22.1%)	37/106 (34.9%)	**RR 0.63** (0.41 to 0.99)	**129 fewer per 1,000** (from 206 fewer to 3 fewer)	⊕⊕◯◯ Low	Critical
Serious adverse events in RCTs - Any serious adverse event												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	serious[a,d]	none	27/147 (18.4%)	33/150 (22.0%)	**RR 0.85** (0.55 to 1.32)	**33 fewer per 1,000** (from 99 fewer to 70 more)	⊕⊕◯◯ Low	Critical
Serious adverse events in RCTs - Withdrawal due to adverse event												
2 Khanna 2016, Khanna 2020	randomised trials	not serious	not serious	not serious	very serious[a,b,c,	none	9/147 (6.1%)	9/150 (6.0%)	**RR 1.03** (0.43 to 2.51)	**2 more per 1,000** (from 34 fewer to 91 more)	⊕◯◯◯ Very low	Critical

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
a. Does not meet optimal information size; single study evidence base
b. Wide confidence intervals
c. Very few events
d. 95% CI includes the line of no difference

Table 34-3: PICO 34: IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first-line ILD treatment; summary of clinical outcomes data in observational studies

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Roofeh, D. et al. 2021[3]	Post-hoc analysis of the focuSSced trial (summarized in RevMan) with stratification performed accordingly to baseline CT involvement	High	mRSS and FVC assessed at baseline and weeks 8, 16, 24, 36, and 48; primary outcome was difference in change from baseline in mRSS at week 48; secondary outcome was difference in distribution of change from baseline to week 48 in FVC % predicted; HAQ-DI, SHAQ, SGRQ, and FACIT-fatigue also assessed at similar time intervals; HRCT planned for all subjects at week 48	210 patients with SSc (with or without ILD), mean age 48.2, 81% female, median disease duration <2 years; patients with FVC <55% predicted or DLCO <45% predicted excluded Participants with minimal interstitial changes without defined ILD were characterized as having no ILD; CT quantitative ILD (QILD) cutoff points were set as minimal (≤5%), mild (>5-10%), moderate (>10-20%), or severe (>20%)	Randomized 1:1 to receive weekly SQ injections of 162 mg toci or placebo for 48 weeks, followed by 48-week, open-label period of toci; of note, immunomodulatory therapy could be added to study medications from week 16 for participants who had a decline in FVC % predicted or from week 24 for those who had worsened skin thickening or other SSc complications	136 patients (65%) with ILD (68 received toci, 68 received placebo) For overall cohort, LSM of FVC % change was -0.1% for TCZ and -6.3% for placebo, $p<0.0001$. For mild, moderate, and severe QILD, the mean±SD change in FVC % in the TCZ arm at 48 weeks were -4.1±2.5% (n=11), 0.7±1.9% (n=19), and 2.1±1.6% (n=26), respectively, and in the placebo group were −10.0±2.6% (n=11), -5.7±1.6% (n=26), and -6.7±2.0% (n=16), respectively. Similar preservation effect in the TCZ arm, which was not present in placebo arm, when stratified according to QLF severity; mean trend over time of FVC % change did not differ based on the extent of QLF for either the TCZ or placebo arm At 48 weeks, overall QILD scores for the TCZ arm showed significant improvement (mean -1.8% [95% CI -3.5, -0.2], p=0.02; patients with >20% QILD showed the largest improvement of any of the subsets (mean -4.9 [95% CI -7.8, -1.9], p=0.01); no statistically significant changes in placebo group across all QILD categories Significant increase in QLF scores at

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						48 weeks in placebo arm (mean 0.7 [95% CI 0.3, 1.1], p=0.00), not seen in TCZ arm (mean -0.5 [95% CI -1.1, 0.2], p=0.12).
Kuster et al. 2022[4]	Eustar cohort study	High	12 months	3273 patients with SSc	93 patients treated with TCZ, 3180 patients treated with standard of care	FVC (predicted): TCZ: 88.7% (95% CI: 83.7 to 93.7) Controls: 87.2% (95% CI: 80.8 to 93.6) Adverse events in 17 (18%) patients on TCZ, occurring in 3 patients after TCZ cessation.

Table 34-4. PICO 34 Excluded Studies

Reference	Reason for Exclusion
Suleman et al. 2021[5]	Wrong study design

References

1. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2020;8(10):963-974. doi:https://dx.doi.org/10.1016/S2213-2600(20)30318-0
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3. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(7):1301-1310. doi:https://dx.doi.org/10.1002/art.41668
4. Kuster S, Jordan S, Elhai M, et al. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD open. 2022;8(2)
5. Suleman Y, Clark KEN, Cole AR, Ong VH, Denton CP. Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase-positive patients. *Rheumatology (Oxford, England)*. 2021;60(8):3945-3946. doi:https://dx.doi.org/10.1093/rheumatology/keab273

PICO 35: In rheumatic disease patients with ILD, what is the impact of JAK inhibitors compared to no JAK inhibitors as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5-associated ILD.[1]
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.[2]

Summary: 2 observational studies indirectly addressed this PICO.
One retrospective study (Fan et al. 2022[1] compared outcomes for MDA5-ILD patients who received tofacitinib (n=26) vs those who received tacrolimus (TAC)(n=35). The 6-month (38.5% vs 62.9%; P = 0.03) and 1-year (44.0% vs 65.7%; P = 0.03) mortality rates in the TOF group were significantly lower than those in the TAC group. Although more patients in the TAC group experienced RP-ILD (22 vs 13), the mortality rates for the TOF group were lower than the TAC group for patients with RP-ILD (76.9% vs 95.5%, P = 0.02 at six months; 84.6% vs 100.0%, p= 0.02 at one year).
In a study by Tardella et al. 2022,[2] 31 RA-ILD patients who received a JAKi and 44 patients who received abatacept were retrospectively studied using a computer-aided method (CaM) to assess changes in (HRCT) fibrosis percentage. Patients were classified as worsened (15% more fibrosis), stable, or improved (15% less fibrosis). After 18 months, 5 (11.4%) patients showed an HRCT deterioration, 32 (72.6%) were considered stable, and 7 (16.0%) patients showed an HRCT improvement in the ABA group. In the JAKis group, 5 (16.1%) patients showed an HRCT deterioration, 20 (64.5%) were considered stable, and 6 (19.4%) patients showed an HRCT improvement. There was no significant change in mean FVC, DLCO, or CT fibrosis scores. Abatacept was not the first-line treatment for this study and patients concomitantly taking methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs) and/or glucocorticoids at a dose of less than 10 mg daily prednisone or equivalent were included.

Table 35-1: impact of JAK inhibitors vs no JAK inhibitors as first line ILD treatment

Author, year	Study design	Risk of bias	Time of reassessment	Population Description	Screening or assessment measures	Results
Fan et al. 2022 [1]	Retrospective observational study	High		MDA5-ILD patients treated with either Tofacitinib or TAC	26 patients were treated with TOF and 35 were treated with TAC	Entire group TOF TAC 6-month mortality 10 (38.5%) 22 (62.9%) P=0.03 1-year mortality 11 (44.0%) 23 (65.7%) p=0.03 RP-ILD TOF TAC 6-month mortality 10 (76.9%) 21 (95.5%) p=0.02 1-year mortality 11 (84.6%) 22 (100%) p=0.02
Tardella et al. 2022 [2]	Retrospective observational study	High		75 RA-ILD patients who received either JAKis or abatacept. Seventy-five patients (69.3% women) were evaluated, 31 received a JAKi while 44 received ABA.	31 patients who received a JAKi and 44 patients who received Abatacept. Computer-aided method (CaM) used to assess changes in (HRCT) fibrosis percentage and classify patients as worsened (15% more), stable, or improved (15% less) fibrosis after 18 months.	Abatacept JAKis Time 0 Time 18 Time 0 Time 18 DLCO 58.69 61.36 59.72 62.77 FVC 82.29 81.24 81.18 79.59 HRCTcam 19.41 18.94 18.54 17.52 All p values NS CT deterioration Stability Improved ABA 5 (11.4%) 32 (72.6%) 7 (16%) JAKis 5 (16%) 20 (65.5%) 6 (19.4%)

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w

PICO 36: In rheumatic disease patients with ILD, what is the impact of daily oral prednisone compared to no daily oral prednisone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 36-1. PICO 36: Excluded Studies

Reference	Reason for exclusion
Peres-Campos et al. 2012[1]	Not a comparator of interest
Behr et al. 1996[2]	Not a comparator of interest
Jensen et al. 2019[3]	Not a comparator of interest
Lu et al. 2018[4]	Population not of interest, wrong study design
Jaafar et al. 2021[5]	Not a comparator of interest
Tzelepis et al. 2007[6]	Does not address PICO 36
Hozumi et al. 2019[7]	Does not address PICO 36
Bodolay et al. 2005[8]	Does not address PICO 36
Deheinzelin et al. 1996[9]	Does not address PICO 36
Friedman et al. 1996[10]	Not a comparator of interest, wrong study design
Behr et al. 1995[11]	Does not address PICO 36
Chen et al. 2022[12]	Does not address PICO 36
Zamora-Legoff et al. 2016[13]	Does not address PICO 36
Adler et al. 2018[14]	Does not address PICO 36

References

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2. Behr J, Vogelmeier C, Beinert T, et al. Bronchoalveolar lavage for evaluation and management of scleroderma disease of the lung. *American journal of respiratory and critical care medicine*. 1996;154(2 Pt 1):400-6.

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PICO 37: In rheumatic disease patients with ILD, what is the impact of IV pulse glucocorticoids compared to no IV pulse glucocorticoids first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 37-1. PICO 37: Excluded Studies

Reference	Reason for exclusion
Tsuji et al. 2020[1]	Not a comparator of interest

References

1. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498.

PICO 38: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to no nintedanib as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- One RCT (SENSCIS[1]) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.
    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022[2]) of another RCT (Flaherty et al., 2019[3]) and (INBUILD[4]) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs ((SENSCIS)(INBUILD)) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS)(INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

Summary:

We included data from two high-quality randomized controlled trials (RCTs; Distler et al., 2019,[1] Flaherty et al., 2019,[3] and Flaherty et al., 2022[4]) and an open-label extension of one of the RCTs (Allanore, et. al., 2022[5]). Pertinent data from these studies were extracted from several subgroup analyses (Matteson et al., 2022[2], Highland et al., 2021,[6] Assassi et al., 2022[7], and Hoffman-Vold et al., 2022[8].

Results from RCTs:

The SENSCIS study is a multicenter, international RCT and is the largest study of SSc-ILD to date in which 576 SSc-ILD patients were randomized 1:1 to 150 mg twice daily of nintedanib vs. placebo.[1] Concomitant treatment with methotrexate or MMF was permitted if on a stable dose for at least 6 months prior to enrollment. 48.4% of patients had been treated with mycophenolate for at least 6 months before enrollment. Notably, subjects were not randomized according to baseline mycophenolate use. 51.9% of patients had diffuse cutaneous systemic sclerosis, and the proportion of participants with diffuse cutaneous systemic sclerosis was modestly higher among those taking mycophenolate at baseline than those who were not. Treatment with other agents, including cyclophosphamide, azathioprine, tacrolimus, tocilizumab, rituximab, or prednisone >10 mg/day (or equivalent) was restricted in the absence of a sufficient washout period.

The INBUILD study is another multicenter, international RCT in which 663 patients with non-idiopathic pulmonary fibrosis (non-IPF) ILD and evidence of ILD progression in the 24 months before screening were randomized 1:1 to 150 mg twice daily of nintedanib vs. placebo.[3,4] Of the 663 patients, 170 were diagnosed with autoimmune ILD and represent the focus of these analyses.[2] Of these 170 patients, 89 had RA-ILD (52.4%), 39 had SSc-ILD (22.9%), 19 had MCTD-ILD (11.2%), and 23 (13.5%) had other autoimmune disease-related ILDs, including 7 with Sjogren's disease-related ILD, 5 with interstitial pneumonia with autoimmune features, 3 with undifferentiated CTD-ILD, 2 with lupus-related ILD, and a total of 5 (n=1 per condition) with either antineutrophil cytoplasmic antibody-associated ILD, microscopic polyangiitis-associated ILD, polymyositis-associated ILD, antisynthetase syndrome, CTD-associated organizing pneumonia, or CTD-ILD. Among the 158 participants with available data, the autoimmune disease diagnosis was confirmed by a rheumatologist in 144 (91.1%). Most participants (n=127; 74.7%) exhibited a usual interstitial pneumonia-like fibrotic pattern on HRCT. Importantly, patients could only be enrolled in this study if they exhibited evidence of ILD progression based on a combination of clinical, pulmonary function, and radiologic criteria "despite management deemed appropriate in clinical practice." The use of several medications at baseline, including mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, rituximab, and oral glucocorticoid >20 mg/day, was restricted and prompted either exclusion from participation or a

washout period. Although data regarding medication use before trial enrollment was not collected, only 4 participants were noted to be using restricted therapies (n=1 for glucocorticoids ≥ 20 mg/day, n=2 for mycophenolate mofetil, n=1 for rituximab; n=0 for the remainder) at baseline. Time since ILD diagnosis based on imaging, the proportion of participants with a UIP-like fibrotic pattern on HRCT, and baseline measures of pulmonary function and self-assessed HRQoL were similar between the nintedanib and placebo groups.

In both RCTs, patients were diagnosed with ILD according to usual practice and exhibited evidence of reticular abnormalities with traction bronchiectasis involving >10% of the lungs on HRCT, [1-4] with FVC % predicted >40%[1] or ≥ 45%,[2-4] and a diffusing capacity of the lung for carbon monoxide (DLCO) (corrected for hemoglobin) that was between 30% and 80%, [2-4] or 90%[1] of the predicted value.

In both RCTs, the primary endpoint was the adjusted annual rate of decline in forced vital capacity (FVC) over 52 weeks. In the SENSCIS study, the adjusted annual rate of change in FVC over 52 weeks was -52.4 mL/year in the nintedanib group vs. -93.3 mL/year in the placebo group (difference: 40.9 mL/year; 95% confidence interval (CI) [3.1, 79.7]; $p = 0.03$).[1] A similar result was observed over the entirety of the SENSCIS trial (100 weeks), with an adjusted annual rate of change in FVC of -54.9 mL/year in the nintedanib group vs. -88.8 mL/year in the placebo group (difference: 33.9 mL/year; 95% CI [3.4, 64.4]; $p = 0.03$).[76] In the SENSCIS study, the treatment effect of nintedanib on the primary outcome was numerically greater in patients who were not taking mycophenolate at baseline (difference: 55.4 mL/year; 95% CI [2.3, 108.5]) compared to those who were on mycophenolate at baseline (difference: 26.3 mL/year; 95% CI [-27.9, 80.5]).[6] Although statistical testing did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups by baseline MMF use ($p = 0.45$), SENSCIS was not powered to detect differences in the primary outcome based on baseline MMF use.

In the INBUILD subgroup analysis by Matteson et al., 2022[2] the adjusted annual rate of change in FVC was -75.9 mL/year in the nintedanib group vs. -178.6 mL/year in the placebo group (difference: 102.7 mL/year; 95% CI [23.9, 181.5]; $p = 0.01$).[2] The treatment effect of nintedanib on the primary outcome was numerically greater in subjects with a UIP-like fibrotic pattern on HRCT (difference: 124.2 mL/year; 95% CI [31.1, 217.3]) than in those with non-UIP-like fibrotic patterns (difference: 41.7 mL/year; 95% CI [-112.2, 195.6]), but statistical testing did not indicate heterogeneity in the treatment effect ($p = 0.37$). The treatment effect of nintedanib on the primary outcome was also numerically greater in subjects on glucocorticoids and/or DMARDs at baseline (difference: 130.5 mL/year; 95% CI [39.5, 221.5]) than in subjects not on glucocorticoids and/or DMARDs at baseline (difference: 17.2 mL/year; 95% CI [-146.8,

181.2]), but statistical testing did not indicate heterogeneity in the treatment effect ($p = 0.24$). Similarly, no heterogeneity was detected in the effect of nintedanib vs. placebo across the subgroups according to autoimmune ILD diagnosis ($p = 0.91$). Importantly this trial was not powered to detect differences in the primary outcome based on (a) the type of fibrotic pattern on HRCT; (b) amongst subgroups based on baseline DMARD and/or glucocorticoid use; or (c) amongst subgroups of autoimmune ILD. The absence of heterogeneity across autoimmune ILD subgroups is also observed in a pooled analysis that incorporates 297 of the 576 participants in SENSCIS that were not on MMF at baseline (as baseline MMF use was prohibited in INBUILD; exploratory interaction $p = 0.84$), even when selectively examining the heterogeneity of treatment effect between RA-ILD and SSc-ILD alone with the exclusion of MCTD-ILD and other fibrosing autoimmune-related ILDs (exploratory interaction $p = 0.52$). Finally, in a pooled analysis of the autoimmune ILD subgroup from the INBUILD trial (regardless of the autoimmune ILD diagnosis) and the SENSCIS trial (regardless of baseline mycophenolate use), the mean difference in the adjusted annual rate of change in FVC over 52 weeks between the nintedanib and placebo groups was 61.8 mL/year (95% CI [4.5, 119.0]).[1-4] The treatment effect of nintedanib on the primary outcome was numerically greater in the INBUILD subgroup analysis than in SENSCIS. [1-4] Statistical testing did not indicate heterogeneity in the treatment effect ($p = 0.17$). Nevertheless, it should be noted that there is considerable heterogeneity between the two trials in the types of autoimmune ILD, the pace of ILD progression, the use of baseline therapies, and the timing of nintedanib use (i.e., as "first line" or not). The certainty of the evidence for this outcome was downgraded largely based on indirectness, as (1) the use of nintedanib in the INBUILD trial was not strictly "first-line"; and (2) patients in INBUILD were required to exhibit evidence of "progressive" autoimmune ILD.

Additional secondary outcomes related to measures of pulmonary function are reported in both RCTs. In pooled analyses incorporating 170 participants with autoimmune ILD from INBUILD and 297 of the 576 participants in SENSCIS that were not on mycophenolate at baseline, the mean difference (in percentage points) in the absolute change in FVC percentage of predicted at week 52 from baseline was 2.14 (95% CI [0.5, 3.8]), favoring nintedanib.[1,4] Similarly, the mean difference (in mL) in the absolute change in FVC at week 52 from baseline was 68.0 mL (95% CI [23.9, 112.0]), favoring nintedanib. The SENSCIS-ON[5] extension trial enrolled a total of 444 patients, accounting for 93.9% of the patients who completed SENSCIS (n=456) or the DDI study (n=17) on treatment, and assessed changes in FVC over 52 weeks in (a) patients who received nintedanib in SENSCIS and continued nintedanib in SENSCIS-ON ("continued nintedanib" group); (b) patients who received placebo in SENSCIS and initiated nintedanib in SENSCIS-ON or who received nintedanib for $\leq$ 28 days in the DDI study ("initiated nintedanib" group). The treatment effect of nintedanib observed in SENSCIS-ON was similar to that observed in SENSCIS, with an adjusted annual rate of change in FVC of -58.3 (SE 15.5) mL in the "continued nintedanib" group and -44.0 (SE 16.2) mL in the "initiated nintedanib" group (-51.3 (SE: 11.2) mL

amongst all patients). The median (minimum, maximum) exposure to nintedanib in SENSCIS-ON was 13.8 (0.2, 13.8) months and did not differ between the "continued nintedanib" and "initiated nintedanib" groups, and the total median (minimum, maximum) exposure to nintedanib across both SENSCIS and SENSCIS-ON was 29.5 (12.8, 37.0) months, thus providing longer-term data on nintedanib treatment. Finally, the use of nintedanib is also favored based on assessments of the proportion of participants exhibiting absolute decline from baseline in FVC of > 5 percentage points at week 52 in SENSCIS, SENSCIS-ON, and over the entirety of the INBUILD trial.[1-5]

Other key secondary endpoints related to HRQoL and mortality did not differ significantly between the nintedanib and the placebo group in either RCT. In the SENSCIS trial, the adjusted mean absolute change in total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52 from baseline did not differ significantly between the trial groups (mean difference: 1.69 (95% CI [-0.74, 4.12]). [1] Longer-term use of nintedanib in the SENSCIS-ON was similarly associated with only modest changes in the SGRQ amongst patients who "continued nintedanib" or "initiated nintedanib", with mean changes from baseline in SGRQ total score at week 52 of +1.37 (SE: 0.87) and -0.31 (SE: 0.91), respectively.[5] In the INBUILD autoimmune ILD subgroup analysis, the mean absolute change in total score on the King's Brief Interstitial Lung Disease (KBILD) questionnaire at week 52 from baseline was also similar between the nintedanib and placebo groups (mean difference: 0.38 [95% CI -2.70 to 3.46]).[2] In SENSCIS, over the 52 weeks, 10 patients in the nintedanib group (3.5%) and 9 patients in the placebo group (3.1%) died (hazard ratio (HR) 1.11, 95% CI [0.46, 2.70]). [1] In the autoimmune-ILD INBUILD subgroup analysis, over the entirety of the INBUILD trial, 8 patients in the nintedanib group (9.8%) and 11 patients in the placebo group (12.5%) died (HR 0.78, 95% CI [0.33, 1.84]).[2]

In terms of adverse events, there were no differences in the proportion of patients with "any adverse event" in the nintedanib group or placebo group in either RCT. However, a pooled analysis indicated a modest, statistically significant increased risk of "any adverse event" with nintedanib use (risk ratio 1.03, 95% CI [1.00, 1.06]). [1-4] Pooled analyses did not identify an increased risk of a severe, serious, or fatal adverse event associated with nintedanib. The most frequently observed adverse events were similar in both RCTs. In SENSCIS, diarrhea was the most common adverse event over the 52 weeks and was observed in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group. In the autoimmune ILD INBUILD subgroup analysis, diarrhea was also the most common adverse event over the entirety of the INBUILD trial and was observed in 63.4% of the patients in the nintedanib group and in 27.3% of those in the placebo group. Notably, a pooled analysis indicated that the "risk of adverse event leading to treatment discontinuation" was higher in the nintedanib group than in the placebo group (risk ratio 1.79, 95% CI [1.21, 2.67]. Diarrhea was the most frequent adverse event leading to treatment discontinuation in both RCTs.[1-4] Longer-term use of nintedanib in the

SENSCIS-ON open-label extension study was also associated with a high frequency of diarrhea and was observed in 304 of 444 (68.5%) patients, and led to the discontinuation of nintedanib in 9 patients (4.6%) in the "continued nintedanib" group and in 53 patients (21.5%) of the "initiated nintedanib" group.[5] More recently, a sex-stratified pooled analysis of patients with autoimmune ILD from INBUILD and patients with SSc-ILD from SENSCIS indicated that the frequency of diarrhea and other adverse events was generally similar between female and male patients treated with nintedanib; however, nausea, vomiting, and elevations in liver function tests were more frequent in female compared to male patients.[8] Adverse events leading to a nintedanib dose reduction were more common in female compared to male patients; however, the proportion of patients with adverse events leading to permanent discontinuation of nintedanib was similar between female and male patients with autoimmune ILD. Importantly, these data did not adjust for the observed differences in baseline body weight between male and female patients, nor did they adjust for the use of anti-diarrheal or antiemetic agents. Ultimately, because heterogeneity in the type of autoimmune ILD, the pace of ILD progression, the timing of nintedanib use, the usage of baseline therapies was felt to have a minimal impact on the adverse event profiles in these RCTs, the certainty of the evidence for these outcomes was not downgraded based on indirectness.

Table 38-1:PICO 38: Nintedanib versus no nintedanib in patients with rheumatic disease-associated ILD (efficacy)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nintedanib	placebo	Relative (95% CI)	Absolute (95% CI)		
Rate of decline in FVC over 52 weeks, adjusted mean +/- SE (mL/year)												
2[a] Distler, et al., 2019[1], Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[c]	not serious	none	369	376	-	MD **61.75 mL/year higher** (4.48 higher to 119.02 higher)	⊕⊕⊕◯ Moderate	Important
Rate of decline in FVC over 52 weeks BY baseline glucocorticoid use, adjusted mean +/- SE (mL/year) - Use of glucocorticoids at baseline – YES												
Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	57	58	-	MD **149.3 mL/year higher** (52.4 higher to 246.2 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY baseline glucocorticoid use, adjusted mean +/- SE (mL/year) - Use of glucocorticoids at baseline – NO

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[e]	none	25	30	-	MD **15.5 mL/year higher** (122.8 lower to 153.8 higher)	⊕⊕◯◯ Low	Important

Rate of decline in FVC over 52 weeks BY baseline DMARD use, adjusted mean +/- SE (mL/year) - Use of DMARDs at baseline – YES

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	36	37	-	MD **163.6 mL/yr higher** (41.7 higher to 285.5 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY baseline DMARD use, adjusted mean +/- SE (mL/year) - Use of DMARDs at baseline – NO

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[f]	none	46	51	-	MD **56.7 mL/year higher** (48.1 lower to 161.5 higher)	⊕⊕◯◯ Low	Important

Rate of decline in FVC over 52 weeks BY baseline DMARD and/or glucocorticoid use, adjusted mean +/- SE (mL/year) - Use of DMARDs and/or glucocorticoids at baseline – YES

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	64	67	-	MD **130.5 mL/year higher** (39.5 higher to 221.5 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY baseline DMARD and/or glucocorticoid use, adjusted mean +/- SE (mL/year) - Use of DMARDs and/or glucocorticoids at baseline – NO

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	18	21	-	MD **17.2 mL/year higher** (146.8 lower to 181.2 higher)	⊕◯◯◯ Very low	Important

Rate of decline in FVC over 52 weeks BY fibrotic pattern on HRCT, adjusted mean +/- SE (mL/year) - Subjects with a UIP-like fibrotic pattern on HRCT

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	62	65	-	MD **124.2 mL/year higher** (31.1 higher to 217.3 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY fibrotic pattern on HRCT, adjusted mean +/- SE (mL/year) - Subjects with other fibrotic patterns on HRCT

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	20	23	-	MD **41.7 mL/year higher** (112.2 lower to 195.6 higher)	⊕◯◯◯ Very low	Important

Rate of decline in FVC over 52 weeks BY type of autoimmune ILD, adjusted mean +/- SE (mL/year) - RA-ILD

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	42	47	-	MD **117.9 mL/year higher** (5.2 higher to 230.6 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY type of autoimmune ILD, adjusted mean +/- SE (mL/year) - SSc-ILD

2[g] Distler, et al., 2019[1], Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	172	164	-	MD **60.97 mL/year higher** (10.18 higher to 111.75 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks BY type of autoimmune ILD, adjusted mean +/- SE (mL/year) - MCTD-ILD

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	7	12	-	MD **31.9 mL/year higher** (210 lower to 273.8 higher)	⊕◯◯◯ Very low	Important

Rate of decline in FVC over 52 weeks BY type of autoimmune ILD, adjusted mean +/- SE (mL/year) - Other fibrosing autoimmune-related ILDs

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	10	13	-	MD **72.5 mL/year higher** (134.1 lower to 279.1 higher)	⊕◯◯◯ Very low	Important

Rate of decline in FVC over 52 weeks in SSc-ILD BY baseline mycophenolate use, adjusted mean +/- SE (mL/year) - YES - Baseline use of mycophenolate mofetil

Highland, et al., 2021[6]	randomized trials	not serious	not serious	not serious	serious[f]	none	138	140	-	MD **26.3 mL/year higher** (27.9 lower to 80.5 higher)	⊕⊕⊕◯ Moderate	Important

Rate of decline in FVC over 52 weeks in SSc-ILD BY baseline mycophenolate use, adjusted mean +/- SE (mL/year) - NO - Baseline use of mycophenolate mofetil

2[h]Highland, et al., 2021[6], Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	172	164	-	MD **60.97 mL/year higher** (10.18 higher to 111.75 higher)	⊕⊕⊕◯ Moderate	Important

Adjusted annual rate of change in FVC at 52 weeks in SSc-ILD, adjusted mean +/- SE (mL/year)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	serious[d]	not serious	none	287	288	-	MD **40.9 mL/year higher** (2.9 higher to 78.9 higher)	⊕⊕⊕◯ Moderate	Important

Adjusted annual rate of change in FVC at 100 weeks in SSc-ILD, adjusted mean +/- SE (mL/year)

Assassi, et al., 2022[7]	randomized trials	not serious	not serious	serious[d]	not serious	none	287	288	-	MD **33.9 mL/year higher** (3.4 higher to 64.4 higher)	⊕⊕⊕◯ Moderate	Important

Absolute change from baseline in FVC% at week 52, adjusted mean +/- SE (%)

2[g] Distler, et al., 2019[1], Matteson, et al., 2022[2]	randomized trials	not serious	not serious	very serious[c]	not serious	none	231	236	-	MD **2.14 higher** (0.45 higher to 3.82 higher)	⊕⊕◯◯ Low	Important

Absolute change from baseline in FVC at week 52, adjusted mean +/- SE (mL)

2[g] Distler, et al., 2019[1], Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[c]	not serious	none	231	236	-	MD **67.96 mL higher** (23.88 higher to 112.03 higher)	⊕⊕⊕◯ Moderate	Important

Absolute change from baseline in DLCO at week 52 in SSc-ILD - % of predicted value

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	serious[f]	none	285	284	-	MD **0.44 lower** (1.94 lower to 1.06 higher)	⊕⊕⊕◯ Moderate	Important

Relative decline from baseline in FVC% >=5% over the whole INBUILD trial, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[f]	none	60/82 (73.2%)	73/88 (83.0%)	**RR 0.88** (0.75 to 1.04)	**10 fewer per 100** (from 21 fewer to 3 more)	⊕⊕◯◯ Low	Important

Patients with SSc-ILD with a relative decline from baseline in FVC, measured in mL, of >5% at week 52 - no./total no. (%)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	not serious	none	95/287 (33.1%)	125/288 (43.4%)	**OR 0.65** (0.46 to 0.91)	**10 fewer per 100** (from 17 fewer to 2 fewer)	⊕⊕⊕⊕ High	Important

Relative decline from baseline in FVC% >=10% over the whole INBUILD trial, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[f]	none	41/82 (50.0%)	55/88 (62.5%)	**RR 0.80** (0.61 to 1.05)	**12 fewer per 100** (from 24 fewer to 3 more)	⊕⊕◯◯ Low	Important

Patients with SSc-ILD with a relative decline from baseline in FVC, measured in mL, of >10% at week 52 - no./total no. (%)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	serious[e]	none	48/287 (16.7%)	52/288 (18.1%)	**OR 0.91** (0.59 to 1.40)	**1 fewer per 100** (from 7 fewer to 6 more)	⊕⊕⊕◯ Moderate	Important

Absolute decline from baseline in FVC% >=5% over the whole INBUILD trial, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	not serious	none	52/82 (63.4%)	69/88 (78.4%)	**RR 0.81** (0.66 to 0.99)	**15 fewer per 100** (from 27 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	Important

Patients with SSc-ILD with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 - no./total no. (%)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	serious[d]	not serious	none	59/287 (20.6%)	82/288 (28.5%)	**OR 0.65** (0.44 to 0.95)	**8 fewer per 100** (from 14 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	Important

Absolute decline from baseline in FVC% >=10% over the whole INBUILD trial, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[e]	none	29/82 (35.4%)	42/88 (47.7%)	**RR 0.74** (0.51 to 1.07)	**12 fewer per 100** (from 23 fewer to 3 more)	⊕⊕◯◯ Low	Important

Patients with SSc-ILD with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 - no./total no. (%)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	serious[e]	none	20/287 (7.0%)	24/288 (8.3%)	**OR 0.82** (0.44 to 1.53)	**1 fewer per 100** (from 4 fewer to 4 more)	⊕⊕⊕◯ Moderate	Important

Absolute change from baseline in King's Brief ILD (KBILD) Questionnaire total score at week 52, adjusted mean +/- SE

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[e]	none	82	88	-	MD **0.38 higher** (2.7 lower to 3.46 higher)	⊕⊕◯◯ Low	Important

Adjusted mean absolute change from baseline in total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52 in SSc-ILD

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	very serious[e]	none	282	283	-	MD **1.69 higher** (0.74 lower to 4.12 higher)	⊕⊕◯◯ Low	Critical

Acute exacerbation of ILD or death, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	10/82 (12.2%)	18/88 (20.5%)	**RR 0.60** (0.29 to 1.22)	**8 fewer per 100** (from 15 fewer to 5 more)	⊕◯◯◯ Very low	Critical

Progression of ILD (absolute decline from baseline in FVC% >=10%) or death, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	serious[e]	none	33/82 (40.2%)	47/88 (53.4%)	**RR 0.75** (0.54 to 1.05)	**13 fewer per 100** (from 25 fewer to 3 more)	⊕⊕◯◯ Low	Important

Death over the whole INBUILD trial, no. (%)

Matteson, et al., 2022[2]	randomized trials	not serious	not serious	serious[d]	very serious[e]	none	8/82 (9.8%)	11/88 (12.5%)	**RR 0.78** (0.33 to 1.84)	**3 fewer per 100** (from 8 fewer to 11 more)	⊕◯◯◯ Very low	Critical

All-cause mortality in SSc-ILD at 52 weeks, no. (%)

Distler, et al., 2019[1]	randomized trials	not serious	not serious	not serious	very serious[i]	none	10/287 (3.5%)	9/288 (3.1%)	**RR 1.11** (0.46 to 2.70)	**0 fewer per 100** (from 2 fewer to 5 more)	⊕⊕◯◯ Low	Critical

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. This is the only efficacy outcome where the data from SENSCIS (Distler 2019) is pooled with that of the autoimmune ILD INBUILD subgroup analysis (Matteson 2022) without selecting for those SENSCIS patients that were NOT on mycophenolate.

b. I^2 for this is 0.48, implying some component of inconsistency. However, the confidence intervals overlap and the point estimates are of similar magnitude, independently statistically significant, and fall on the same side of the "no-effect" line. Finally, the p-value for heterogeneity is > 0.05. Therefore, this was not downgraded.
c. Indirectness stems from the study populations in each RCT relative to the posed PICO question. The INBUILD methodology implies that nintedanib is NOT being used as "first-line" therapy for treating ILD in patients with rheumatic disease. The certainty of the evidence was therefore downgraded.
d. Indirectness stems from the discrepancy between the intervention group in this study and the PICO question. The study methodology of INBUILD implies that nintedanib is NOT being used as a "first-line" therapy for treating ILD in patients with rheumatic disease but rather as adjunctive therapy in patients with progressive ILD. The certainty of the evidence was therefore downgraded.
e. Wide confidence interval with a possible benefit that reflects the fact that the original trial was not powered adequately to detect differences based on this subgroup analysis.
f. Confidence interval includes appreciable benefit.
g. The data from SENSCIS (Highland 2021) is being used here to provide additional data regarding patients with SSc-ILD who received nintedanib (ONLY the n=297 patients from SENSCIS that were NOT on mycophenolate mofetil at baseline).
h. Data from SSc-ILD (n=39) from the INBUILD trial is included.
i. Wide confidence interval with possible harm that reflects the fact that the original trial was not powered adequately to detect differences based on this subgroup analysis.

Table 38-2: PICO 38: Nintedanib versus no nintedanib in patients with rheumatic disease-associated ILD (adverse events)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nintedanib	placebo	Relative (95% CI)	Absolute (95% CI)		
Any adverse event, no. (%)												
2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	Serious[e]	none	362/370 (97.8%)	355/376 (94.4%)	**RR 1.03** (1.00 to 1.06)	**28 more per 1,000** (from 0 fewer to 57 more)	⊕⊕⊕◯ Moderate	Important
Diarrhea, no. (%)												
2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	Serious[e]	none	270/370 (73.0%)	115/376 (30.6%)	**RR 2.38** (2.02 to 2.81)	**42 more per 100** (from 31 more to 55 more)	⊕⊕⊕◯ Moderate	Important
Nausea, no. (%)												
2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	Serious[e]	none	113/370 (30.5%)	49/376 (13.0%)	**RR 2.34** (1.73 to 3.17)	**17 more per 100** (from 10 more to 28 more)	⊕⊕⊕◯ Moderate	Important
Vomiting, no. (%)												
2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	Serious[e]	none	85/370 (23.0%)	36/376 (9.6%)	**RR 2.39** (1.66 to 3.43)	**13 more per 100** (from 6 more to 23 more)	⊕⊕⊕◯ Moderate	Important

Abdominal pain, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	Serious[a]	not serious	serious[b]	none	43/370 (11.6%)	23/376 (6.1%)	**RR 2.36** (0.76 to 7.35)	**8 more per 100** (from 1 fewer to 39 more)	⊕⊕◯◯ Low	Important

Decrease in weight, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[c]	none	44/370 (11.9%)	13/376 (3.5%)	**RR 3.83** (1.28 to 11.42)	**10 more per 100** (from 1 more to 36 more)	⊕⊕⊕◯ Moderate	Important

Increase in AST, no. (%)

1 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[b, e]	none	11/82 (13.4%)	4/88 (4.5%)	**RR 2.95** (0.98 to 8.90)	**9 more per 100** (from 0 fewer to 36 more)	⊕⊕◯◯ Low	Important

Increase in ALT, no. (%)

1 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[c, e]	none	14/82 (17.1%)	3/88 (3.4%)	**RR 5.01** (1.49 to 16.80)	**14 more per 100** (from 2 more to 54 more)	⊕⊕◯◯ Low	Important

Severe adverse event, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[b]	none	65/370 (17.6%)	52/376 (13.8%)	**RR 1.21** (0.75 to 1.94)	**29 more per 1,000** (from 35 fewer to 130 more)	⊕⊕⊕◯ Moderate	Important

Serious adverse events, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[d]	none	97/370 (26.2%)	90/376 (23.9%)	**RR 1.10** (0.86 to 1.41)	**24 more per 1,000** (from 34 fewer to 98 more)	⊕⊕⊕◯ Moderate	Critical

Fatal adverse event, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	serious[b]	none	8/370 (2.2%)	8/376 (2.1%)	**RR 1.03** (0.39 to 2.73)	**1 more per 1,000** (from 13 fewer to 37 more)	⊕⊕⊕◯ Moderate	Critical

Adverse event leading to treatment discontinuation, no. (%)

2 Distler, 2019 Matteson, 2022	randomised trials	not serious	not serious	not serious	Serious[e]	none	60/370 (16.2%)	34/376 (9.0%)	**RR 1.79** (1.21 to 2.67)	**71 more per 1,000** (from 19 more to 151 more)	⊕⊕⊕◯ Moderate	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

a. I^2 of 57% for this outcome.

b. 95% CI includes the line of no difference, and potential of appreciable harm

c. 95% CI includes the potential for appreciable harm

d. 95% CI includes the line of no difference

e. single study, doesn't meet optimal information size

Other Data Presented:

Other outcomes assessed in the SENSCIS trial[1] included the difference in absolute change from baseline in score on the HAQ-DI 0.032 (95% CI, −0.035 to 0.099) and score on the FACIT–Dyspnea questionnaire 0.64 (95% CI, −0.51 to 1.79) at week 52; and the time to death from any cause (analyzed over the entire trial period) -Over 52 weeks, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died (hazard ratio, 1.16; 95% CI, 0.47 to 2.84).

One SENSCIS sub-analysis, Seibold et al., 2020[9], showed that AEs associated with nintedanib in patients with SSc-ILD are similar across subgroups defined by age, sex, race, and weight. Diarrhea led to permanent treatment discontinuation in 6.9% and 0.3% of patients in the nintedanib and placebo groups, respectively. In the nintedanib and placebo groups, respectively, 48.3% and 12.2% of patients had ≥1 dose reduction and/or treatment interruption, and adverse events leading to permanent discontinuation of the trial drug in 16.0% and 8.7% of patients. The rate of decline in FVC was similar in nintedanib-treated patients, irrespective of dose adjustments used to manage AEs. Overall, this study showed that dose adjustments (interruption for < 4 weeks or reduction to 100 mg BID) used

to manage AEs in the SENSCIS trial can be implemented in clinical practice to minimize the impact of AEs and help patients with SSc-ILD remain on nintedanib. The adverse event profile of nintedanib over 100 weeks was consistent with that observed over 52 weeks.[7] Overall, the most commonly reported AEs with nintedanib were GI and liver disorder events; most were mild-to-moderate in severity, similar to that observed in patients with IPF.

In another subanalysis of the SENSCIS trial,[10] response to treatment was compared in subgroups with and without cough or dyspnea at baseline (defined by responses to the St George's Respiratory Questionnaire). At baseline, 114/575 patients (19.8%) did not have a cough, and 172/574 patients (30.0%) did not have dyspnea. In the placebo group, the rate of FVC decline over 52 weeks was similar in patients with and without cough (-95.6 and -83.4 mL/year, respectively) or dyspnea (-95.8 and -87.7 mL/year). The effect of nintedanib vs. placebo on reducing the rate of FVC decline was numerically more pronounced in patients without than with cough [difference: 74.4 (95% CI -11.1, 159.8) vs. 31.5 (-11.1, 74.1)] and without than with dyspnea [79.8 (9.8, 149.7) vs. 25.7 (-19.9, 71.3)], but interaction p-values did not indicate heterogeneity in the treatment effect between these subgroups (p=0.38 and p=0.20, respectively). Patients with cough or dyspnea at baseline also had a numerically greater extent of fibrotic ILD and numerically lower FVC % predicted than patients without dyspnea or cough. Overall, in the placebo group of the SENSCIS trial, the rate of FVC decline was similar irrespective of the presence of cough or dyspnea at baseline. The effect of nintedanib on reducing the rate of FVC decline was numerically more pronounced in patients without than with cough or dyspnea at baseline but not statistically significantly different between the subgroups.

SENSCIS subgroup analysis[11] also assessed if a reduction in the annual rate of decline in FVC among SSc-ILD patients receiving nintedanib vs. placebo was different based on their Anti-Topo + status, Skin subtype (diffuse vs. limited) or MRSS (below or above 18). At baseline, 60.8% of 576 patients who received treatment with either nintedanib or placebo were positive for ATA, 51.9% had dcSSc, and 77.5% of 574 patients with MRSS data available had an MRSS of <18. The effect of nintedanib versus placebo on reducing the rate of decline in FVC (ml/year) was numerically more pronounced in ATA-negative patients compared to ATA-positive patients (adjusted difference in the rate of FVC decline, 57.2 ml/year [95% CI –3.5, 118.0] versus 29.9 ml/year [95% CI –19.1, 78.8]), in patients with a baseline MRSS ≥18 compared to those with a baseline MRSS of <18 (adjusted difference in the rate of FVC decline, 88.7 ml/year [95% CI 7.7, 169.8] versus 26.4 ml/year [95% CI –16.8, 69.6]), and in patients with dcSSc compared to those with lcSSc (adjusted difference in the rate of FVC decline, 56.6 ml/year [95% CI 3.2, 110.0] versus 25.3 ml/year [95% CI –28.9, 79.6]). However, all exploratory interaction p values were nonsignificant (all p > 0.05), indicating no heterogeneity in the effect of nintedanib versus placebo between these subgroups of patients.

An additional subanalysis of SENSCIS data showed that nintedanib had the same effect on slowing FVC decline in Asians (difference, 44.3 mL/year [95% CI: -32.8, 121.4]) vs. non-Asian patients (difference, 39.0 mL/year [95% CI: -5.1, 83.1]) (treatment-by-time-by-subgroup interaction, p= 0.91), with similar AE profile.[12]

Further, in Japanese patients, a subanalysis[1311] showed that the adjusted annual rate of FVC decline over 52 weeks was –86.2mL/year (nintedanib) and –90.9mL/year (placebo); treatment difference, 4.67 mL/year (95% CI, -103.28, 112.63) with no heterogeneity in t/t effect between Japanese and non-Japanese patients (treatment-by-visit-by-subgroup interaction; p=0.49).

[*Note: This data is included in the GRADE table and is noted in the "Summary" text*] In a SENSCIS post hoc analysis,[14,15] Nintedanib was also shown to have a clinically relevant benefit on the progression of SSc-ILD. The proportions of subjects with categorical changes in FVC % predicted at week 52 and the time to absolute decline in FVC of ≥5% predicted or death, and absolute decline in FVC of ≥10% predicted or death were assessed. At week 52, in subjects treated with nintedanib and placebo, respectively:

- 55.7% and 66.3% had any decline in FVC % predicted,
- 13.6% and 20.1% had a decline in FVC of >5% to ≤10% predicted,
- 3.5% and 5.2% had a decline in FVC of >10% to ≤15% predicted,
- 34.5% and 43.8% had a decrease in FVC of ≥3.3% predicted (proposed minimal clinically important difference [MCID] for worsening of FVC),
- 23.0% and 14.9% had an increase in FVC of ≥3.0% predicted (proposed MCID for improvement in FVC).

Over 52 weeks, the hazard ratio (HR) for an absolute decline in FVC of ≥5% predicted or death with nintedanib versus placebo was 0.83 (95% confidence interval [95% CI] 0.66−1.06) (p = 0.14), and the HR for an absolute decline in FVC of ≥10% predicted was 0.64 (95% CI 0.43−0.95) (p = 0.029).

Table 38-1. PICO 38 Excluded Studies

Reference	Reasons for exclusion
Inoue et al., 2021[16]	No population of interest
Brown et al., 2020[17]	No comparator of interest
Wells et al., 2020[15]	No population of interest

Reference	Reasons for exclusion
Maher et al., 2022[18]	Does not address PICO 38
Cottin et al., 2021[19]	No population of interest
Goos et al., 2021[20]	No outcomes of interest
Kreuter et al., 2022[21]	No comparator of interest
Kreuter et al., 2022 [22]	Wrong study design
Bonella et al., 2022[23]	No population of interest
Ogura et al., 2022[24]	Wrong publication type
Denton et al., 2022[25]	Wrong publication type
Maher et al., 2022[26]	No comparator of interest

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PICO 39: In rheumatic disease patients with ILD, what is the impact of pirfenidone compared to no pirfenidone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition, hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.
- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated based on an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

Summary: We found evidence to address this PICO from 3 RCTs.[1-3]

First, we include a small proof of concept/pilot study, Acharya et al., 2020.[1] This double-blind RCT study examined pirfenidone (n=16) vs. placebo (n=13) in SSc-ILD patients and failed to achieve its primary endpoint with no difference in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months in the pirfenidone vs. placebo groups. It also failed to find a significant beneficial effect of pirfenidone over placebo in improving exercise capacity or respiratory symptoms. This study was underpowered to provide conclusive evidence. However, only one subject (5.9%) had worsening lung functions in the pirfenidone group, compared to 4 (23.5%) subjects in the placebo group, but not statistically significantly different. In subjects with a UIP pattern on HRCT, 5/6 (83.3%) receiving pirfenidone remained stable vs. only 2/5 (40%) subjects in the placebo group remained stable, suggesting a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.

Secondly, we include Solomon et al., 2022[2], a phase 2 RCT (TRAIL1) (n=123) in RA-ILD. Patients were randomly assigned (1:1) to receive 2403 mg oral pirfenidone or placebo daily. The trial was stopped early (March 31, 2020) due to slow recruitment and the

COVID-19 pandemic. The difference in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death) between the two groups was not significant (seven [11%] of 63 patients in the pirfenidone group vs. nine [15%] of 60 patients in the placebo group; OR 0.67 [95% CI 0.22 to 2.03]; p=0.48). See **Table 39-1.**

Compared with the placebo group, patients in the pirfenidone group had a slower rate of decline in lung function, measured by the estimated annual change in absolute FVC (–66 vs. –146; p=0.0082) and FVC% (–1.02 vs. –3.21; p=0.0028). In addition, 34 (54%) of 63 patients with usual interstitial pneumonia in the pirfenidone group had a significantly smaller reduction in annual change in FVC at 52 weeks compared with 47 (78%) of 60 patients with usual interstitial pneumonia in the placebo group (–43 mL vs. –169 mL; p=0.0014).
The groups were similar with regards to the decline in FVC% by 10% or more (five [8%] participants in the pirfenidone group vs. seven [12%] in the placebo group; OR 0.52 [95% CI 0.14–1.90]; p=0.32) and the frequency of progression as defined by OMERACT (16 [25%] in the pirfenidone group vs. 19 [32%] in the placebo group; OR 0.68 [0.30–1.54]; p=0.35).

While there were more treatment-emergent AEs in the pirfenidone group and treatment-related AEs leading to drug discontinuation in the pirfenidone arm, these were mild grade 1, and most common were GI side effects (nausea). There was no significant difference in the treatment-emergent serious adverse events rate between the two groups, and there was no difference in treatment-related deaths.

Thirdly, we include Behr et al[3], a multicenter, double-blind, randomized, placebo-controlled, parallel phase 2b trial (RELIEF) which randomly assigned 127 patients (1:1) to either oral pirfenidone (n=64)(267 mg three times per day in week 1, 534 mg three times per day in week 2, and 801 mg three times per day thereafter) or matched placebo (n=63), added to their ongoing medication for progressive fibrotic ILD due to 4 diagnoses: collagen or vascular diseases (i.e., connective tissue disease-associated ILDs), fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis. The study was prematurely terminated at 48 weeks based on an interim analysis for futility triggered by slow recruitment. This caused a failure to achieve the intended power, and caused a high number of missing values as patients did not complete the trial as planned. Despite this, a treatment effect was noted in prespecified primary endpoint analysis. A significantly lower decline in FVC % predicted in the pirfenidone group was noted compared with placebo (p=0·043); the result was similar when the model was stratified by diagnostic group (p=0·042). The study suggested that in patients with fibrotic ILDs other than IPF who deteriorate despite conventional therapy, adding pirfenidone to existing treatment might attenuate disease progression as measured by a decline in FVC.

In the analyses of secondary endpoints, no significant difference was found between the pirfenidone and placebo groups with regard to progression-free survival.

The safety and tolerability profile of pirfenidone was similar to that described in previous IPF trials. One death (non-respiratory) occurred in the pirfenidone group (2%) and five deaths (three of which were respiratory) occurred in the placebo group (8%). The most frequent serious adverse events in both groups were infections and infestations (5 [8%] in the pirfenidone group, 10 [16%] in the placebo group); disease worsening (two [3%] in the pirfenidone group, seven [11%] in the placebo group); and cardiac disorders (one ([2%] in the pirfenidone group, 5 [8%] in the placebo group). Adverse events (grade 3–4) of nausea (two patients on pirfenidone, two on placebo), dyspnea (one patient on pirfenidone, one on placebo), and diarrhea (one patient on pirfenidone) were also observed.

Table 39-1. PICO 39: Pirfenidone vs. no pirfenidone for first-line treatment of rheumatic disease patients with ILD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pirfenidone	No pirfenidone	Relative (95% CI)	Absolute (95% CI)		
GI Adverse events (n/v/d) in SSc-ILD												
Achayara et al., 2020[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/16 (50.0%)	5/17 (29.4%)	**RR 1.70 (0.70 to 4.12)**	**206 more per 1,000 (from 88 fewer to 918 more)**	⊕⊕◯◯ Low	Critical
RA-ILD Patients meeting Composite endpoint (decline in FVC% > 10% or death), at 52-weeks												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	serious[e]	serious[d]	none	7/63 (11.1%)	9/60 (15.0%)	**RR 0.74 (0.29 to 1.86)**	**39 fewer per 1,000 (from 107 fewer to 129 more)**	⊕◯◯◯ Very low	Important
Estimated annual change in absolute FVC at 52 weeks (RA-ILD)												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	serious[e]	serious[d]	none	63	60	-	SMD **0.48 higher (0.12 higher to 0.84 higher)**	⊕◯◯◯ Very low	Important
Estimated annual change in absolute FVC (ml) in UIP (RA-ILD)												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	serious[e]	serious[d]	none	63	60	-	MD **126 higher (49.16 higher to 202.84 higher)**	⊕◯◯◯ Very low	Important
Decline in FVC (% pred) by 10% or greater (RA-ILD)												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	serious[e]	serious[d]	none	5/63 (7.9%)	7/60 (11.7%)	**RR 0.68 (0.23 to 2.03)**	**37 fewer per 1,000 (from 90 fewer to 120 more)**	⊕◯◯◯ Very low	Important
All cause Mortality at 52 weeks (RA-ILD)												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	not serious	serious[d]	none	2/63 (3.2%)	3/60 (5.0%)	**RR 0.63 (0.11 to 3.67)**	**19 fewer per 1,000 (from 45 fewer to 134 more)**	⊕⊕◯◯ Low	Critical
All cause hospitalization at 52 weeks (RA-ILD)												
Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	not serious	serious[d]	none	7/63 (11.1%)	7/60 (11.7%)	**RR 0.95 (0.36 to 2.55)**	**6 fewer per 1,000 (from 75 fewer to 181 more)**	⊕⊕◯◯ Low	Critical

Respiratory exacerbations requiring hospitalization at 52 weeks (RA-ILD)

Solomon et al., 2022[2]	randomised trials	serious[c]	not serious	not serious	serious[d]	none	1/63 (1.6%)	2/63 (3.2%)	**RR 0.50 (0.05 to 5.38)**	**16 fewer per 1,000 (from 30 fewer to 139 more)**	⊕⊕◯◯ Low	Critical

T/t emergent AEs asso with Discontinuing the drug at 52 weeks (RA-ILD)

Solomon et al., 2022[2]	randomised trials	not serious	not serious	not serious	serious[d]	none	15/62 (24.2%)	6/60 (10.0%)	not estimable	**140 fewer per 1,000 (from 270 fewer to 10 fewer)**	⊕⊕⊕◯ Moderate	Critical

Treatment emergent AEs at 52 weeks (RA-ILD)

Solomon et al., 2022[2]	randomised trials	not serious	not serious	not serious	serious[d]	none	62/62 (100.0%)	56/60 (93.3%)	**RR 1.07 (0.99 to 1.15)**	**65 more per 1,000 (from 9 fewer to 140 more)**	⊕⊕⊕◯ Moderate	Critical

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

Explanations

- **a.** Convenience sampling due to low availability of drug - required 64 subjects for optimal power. But planned recruitment of 34.
- **b.** Small N of 17 in both arms of the study
- **c.** Selection bias with an inclusion criterion of at least 10% fibrosis on HRCT; results in unknown applicability of findings to patients with less fibrosis Very stringent pulmonary physiology criteria of >10% FVC deterioration. Only 12% of patients in the placebo group had a decline of 10% or more in FVC over 1 year. Typically >5% considered meaningful clinically.
- **d.** Small N in both arms
- **e.** Surrogate outcome for mortality

Table 39-2. PICO 39 Excluded Studies

Reference	Reason for Exclusion
Li et al., 2016 [4]	No comparator of interest
Wang et al., 2022 [5]	No intervention of interest

References

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270

3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3
4. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Scientific reports*. 2016;6:33226. doi:https://dx.doi.org/10.1038/srep33226
5. Wang J, Wang X, Qi X, et al. The Efficacy and Safety of Pirfenidone Combined With Immunosuppressant Therapy in Connective Tissue Disease-Associated Interstitial Lung Disease: A 24-Week Prospective Controlled Cohort Study. *Frontiers in medicine*. 2022;9:871861. doi:https://dx.doi.org/10.3389/fmed.2022.871861

PICO 40: In rheumatic disease patients with ILD, what is the impact of IVIG compared to no IVIG as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 40-1. PICO 40: Excluded Studies

Reference	Reason for exclusion
Danieli et al. 2014[1]	No treatment of interest
Wang et al. 2022[2]	No treatment or population of interest

References

1. Danieli MG, Gambini S, Pettinari L, Logullo F, Veronesi G, Gabrielli A. Impact of treatment on survival in polymyositis and dermatomyositis. A single-centre long-term follow-up study. *Autoimmunity reviews*. 2014;13(10):1048-54.
2. Wang LM, Yang QH, Zhang L, et al. Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Rheumatology (Oxford, England)*.

PICO 41: In rheumatic disease patients with ILD, what is the impact of plasma exchange compared to no plasma exchange as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

Summary:

We included one low-quality observational study.[1]

Results from one observational study (n=19) showed improved survival at 1 year among CADM patients with refractory ILD treated with PE (n=11) vs. those not treated with PE (n=8) (see Table 41-1).[1] No difference was reported between groups in rates of bacterial infection (75% no PE vs. 64% PE treated), fungal infection (50% no PE vs. 18% PE treated), cytomegalovirus infection (50% no PE vs 18% PE treated), and *Pneumocystis jirovetii* pneumonia (13% no PE vs. 0% PE treated). This study indirectly addresses this PICO since PE was not a first-line treatment. In addition, this study was conducted over the course of 15 years (2005 to 2020) during which treatment patterns varied over time and could impact survival.

Table 41-1:PICO 41: Plasma exchange vs no plasma exchange as first line ILD treatment

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Komai et al., 2021[1]	Retrospective observational case control study to compare survival and clinical outcomes among patients treated with and without plasma exchange	High Risk – small size, single center study. Selection bias: therapeutic regimens depended on the decision of clinicians. Not randomized. Long duration over which study was conducted	1 year	19 CADM-ILD patients refractory to combination therapy of high-dose glucocorticoids, calcineurin inhibitors, and cyclophosphamide	11 of 19 patients were further treated with plasma exchange 1-3 times/week; median 17	Combination therapy with therapeutic PE associated with an improved cumulative survival at 1 year (91% and 50%, respectively, $p < 0.05$), in refractory ILD in CADM patients. Among PE-treated patients, anti-MDA-5 antibody titre, ferritin, and KL-6 as serological activity

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
		(2005-2020). Treatment patterns varied over time, including use of biologics 2017 onwards which could impact survival. High attrition. Among the 19 patients, four patients died from respiratory failure despite treatment with high-dose steroids, IVCYC, calcineurin inhibitors, and other medical interventions, and one died from opportunistic infection.				markers were sustainably reduced only after initiating PE. Therapeutic intervention with PE reduced the frequency of exacerbation of ILD requiring methylprednisolone pulse therapy. The occurrence of bacterial, fungal, and cytomegalovirus infection did not differ between the groups with and without PE, and adverse events associated with PE resolved with appropriate intervention. <u>Rates based on 8 patients not treated with PE vs 11 patients treated with PE:</u> Bacterial infection: 75% vs 64% Fungal infection: 50% vs 18% Cytomegalovirus infection: 50% vs 64% *Pneumocystis jirovetii* pneumonia: 13% vs 0%

Table 41-2. PICO 41: Excluded Studies

References	Reasons for exclusion
Tsuji et al., 2020[2]	Wrong study design

Table 41-2: Additional resources to consider

Reference	Notes
Shirakashi et al., 2020[3]	Suggested by Michael George. Study more directly addresses PICO 238 (RP-ILD).

Abe et al., 2020[4]	Suggested by Michael George. Study more directly addresses PICO 238 (RP-ILD).

References

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7. doi:https://dx.doi.org/10.1080/03009742.2021.1995984
2. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
3. Shirakashi M, Nakashima R, Tsuji H, et al. Efficacy of plasma exchange in anti-MDA5-positive dermatomyositis with interstitial lung disease under combined immunosuppressive treatment. *Rheumatology (Oxford, England)*. 2020;59(11):3284-3292. doi:https://dx.doi.org/10.1093/rheumatology/keaa123
4. Abe Y, Kusaoi M, Tada K, Yamaji K, Tamura N. Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy. *Rheumatology (Oxford, England)*. 2020/04// 2020;59(4):767-771. doi:10.1093/rheumatology/kez357

PICO 42: In rheumatic disease patients with ILD without ILD progression, what is the impact of adding nintedanib to mycophenolate compared to not adding nintedanib to mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings: A subgroup analysis of 279 individuals taking mycophenolate in the SENSCIS trial (nintedanib vs. placebo) **indirectly** addresses PICO 42. At 52 weeks follow-up, no significant difference was reported in the annual rate of decline in FVC (difference 26.3, 95% CI: -27.9 to 80.6) or change in SGRQ total score (1.6, 95% CI: -1.86 to 5.06). The adverse event profile was similar.

Summary: 1 RCT Highland et al., 2021[1] addressed this PICO.

We include evidence from a subgroup analysis of 1 large-high-quality double-blind RCT (Highland et al., 2021, using data from the SENSCIS Trial)[1] in which 576 SSc-ILD patients were enrolled, randomly assigned to, and treated with nintedanib (n=288) or placebo (n=288). A prespecified primary endpoint analysis assessed outcomes by mycophenolate use at baseline. Note, patients were not randomized to MMF.

139 (48%) of 288 in the nintedanib group and 140 (49%) of 288 in the placebo group were taking mycophenolate at baseline. In patients taking mycophenolate at baseline, the adjusted mean annual rate of decline in FVC was – 40.2 mL per year (SE 19.8) with nintedanib and –66.5 mL per year (SE 19.3) with placebo (difference: 26.3 mL per year [95% CI –27.9 to 80.6]) at 52 weeks (see Table 42-1). No heterogeneity was found in the effect of nintedanib versus placebo on the annual rate of decline in FVC between the subgroups by mycophenolate use (p-value for interaction=0.45). In patients taking mycophenolate at baseline, the adjusted absolute change from baseline in SGRQ total score at week 52 was 0.7 (SE 1.3) with nintedanib and –0.9 (SE 1.2) with placebo (difference: 1.6 [95% CI –1.86 to 5.06]).

The adverse event profile of nintedanib was similar between the 2 groups. Diarrhea, the most common adverse event, was reported in 106 (76%) of 139 patients in the nintedanib group and 48 (34%) of 140 in the placebo group among those taking mycophenolate at baseline.

Overall, nintedanib, in combination with mycophenolate, provided greater numerical preservation of lung function than MMF alone. The combination of mycophenolate and nintedanib offers a safe treatment option for patients with SSc-ILD. More data are needed on the benefits of initial combination therapy versus a sequential approach to the treatment of SSc-ILD, which were not assessed by this study.

Table 42-1: PICO 42: Nintedanib + MMF vs. MMF in SSc-ILD (indirectly addresses)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nintedanib + MMF	No Nintedanib + MMF	Relative (95% CI)	Absolute (95% CI)		
Adjusted annual rate of decline in FVC over 52 weeks, mL per year												
Highland et al., 2021	randomised trials	not serious	not serious	serious [a]	serious[b]	none	139	140	-	MD 26.3 higher (27.9 lower to 80.6 higher)	⊕⊕◯◯ Low	Important
Adjusted absolute change from baseline in SGRQ total score at week 52												
Highland et al., 2021[1]	randomised trials	not serious	not serious	not serious	serious[b]	none	139	140	-	MD 1.60 higher (1.86 lower to 5.06 higher)	⊕⊕◯◯ Low	Critical
Adverse events, Any												
Highland et al., 2021[1]	randomised trials	not serious	not serious	not serious	serious[b]	none	136/139 (97.8%)	135/140 (96.4%)	**RR 1.01 (0.97 to 1.06)**	**10 more per 1,000 (from 29 fewer to 58 more)**	⊕⊕◯◯ Low	Critical
Adverse events, Serious												
Highland et al., 2021[1]	randomised trials	not serious	not serious	not serious	serious[b]	none	36/139 (25.9%)	22/140 (15.7%)	**RR 1.65 (1.02 to 2.65)**	**102 more per 1,000 (from 3 more to 259 more)**	⊕⊕◯◯ Low	Critical
Adverse Events Leading to Treatment Discontinuation												
Highland et al., 2021[1]	randomised trials	not serious	not serious	not serious	Serious[b,c]	none	15/139 (10.8%)	9/140 (6.4%)	**RR 1.68 (0.76 to 3.71)**	**44 more per 1,000 (from 15 fewer to 174 more)**	⊕⊕◯◯ Low	Important

CI: confidence interval; **RR:** risk ratio; **SMD:** standardized mean difference

Explanations

Subgroup analysis providing indirect evidence

- **a.** Surrogate outcome for mortality
- **b.** <200 patients per arm; single study evidence base
- **c.** Wide confidence intervals

Table 42-2. PICO 42 Excluded studies

Reference	Reason for exclusion
Allanore et al. 2022[2]	No relevant comparator of interest
Hoffmann-Vold et al. 2022[3]	No relevant comparator of interest

References for PICO 42

1. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1
2. Allanore Y, Vonk MC, Distler O, et al. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Annals of the rheumatic diseases*. 2022;81(12):1722-1729. doi:https://protect-us.mimecast.com/s/7ceMCo2ON1fr7GPkHwiRPo?domain=dx.doi.org
3. Hoffmann-Vold AM, Volkmann ER, Allanore Y, et al. Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials. *The Lancet Rheumatology*. 2022;4(10):e679-e687. doi:https://protect-us.mimecast.com/s/cq22CADmJpCNvoljT2Eb4ry?domain=dx.doi.org

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076
2. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681
4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020
5. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1
6. Assassi S, Distler O, Allanore Y, et al. Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial. *ACR Open Rheumatology*. 2022;doi:https://dx.doi.org/10.1002/acr2.11483
7. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. *Annals of the rheumatic diseases*. 2020;79(11):1478-1484. doi:https://dx.doi.org/10.1136/annrheumdis-2020-217331
8. Volkmann ER, Kreuter M, Hoffmann-Vold AM, et al. Dyspnoea and cough in patients with systemic sclerosis-associated interstitial lung disease in the SENSCIS trial. *Rheumatology (Oxford, England)*. 2022;doi:https://dx.doi.org/10.1093/rheumatology/keac091
9. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
10. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory investigation*. 2021;59(2):252-259. doi:https://dx.doi.org/10.1016/j.resinv.2020.10.005
11. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402

12. Maher TM, Mayes MD, Kreuter M, et al. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(4):671-676. doi:https://dx.doi.org/10.1002/art.41576

PICO 43: In rheumatic disease patients with ILD without ILD progression, what is the impact of adding pirfenidone to mycophenolate compared to not adding pirfenidone to mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 43, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 39 (pirfenidone vs no pirfenidone as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Moderate for PICO 25 and Low for PICO 39. An additional downgrade due to indirect comparison for PICO 43 resulted in a rating of Low (for mycophenolate) to Very low (for pirfenidone).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.

- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 39: direct evidence from 3 RCTs

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition,

hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.

- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 39.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 39

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270

3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3

PICO 44: In rheumatic disease patients with ILD, what is the impact of upfront combination of nintedanib with mycophenolate compared to mycophenolate alone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 44, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 38 (nintedanib vs no nintedanib as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Moderate to Low for PICO 38. An additional downgrade due to indirect comparison for PICO 44 resulted in a rating of Very low.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.
    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs ((SENSCIS)(INBUILD)) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS)(INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 38.

Table 44-1. PICO 44: Excluded Studies

Reference	Reason for exclusion
Kreuter et al. 2022[1]	Wrong study design

References for PICO 44

1. Kreuter M, Del Galdo F, Miede C, et al. Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis. *Arthritis research & therapy*. 2022;24(1):19.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076
2. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681
4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020
5. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1

6. Assassi S, Distler O, Allanore Y, et al. Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial. *ACR Open Rheumatology*. 2022;doi:https://dx.doi.org/10.1002/acr2.11483
7. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. *Annals of the rheumatic diseases*. 2020;79(11):1478-1484. doi:https://dx.doi.org/10.1136/annrheumdis-2020-217331
8. Volkmann ER, Kreuter M, Hoffmann-Vold AM, et al. Dyspnoea and cough in patients with systemic sclerosis-associated interstitial lung disease in the SENSCIS trial. *Rheumatology (Oxford, England)*. 2022;doi:https://dx.doi.org/10.1093/rheumatology/keac091
9. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
10. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory investigation*. 2021;59(2):252-259. doi:https://dx.doi.org/10.1016/j.resinv.2020.10.005
11. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402
12. Maher TM, Mayes MD, Kreuter M, et al. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(4):671-676. doi:https://dx.doi.org/10.1002/art.41576
13.

PICO 45: In rheumatic disease patients with ILD, what is the impact of upfront combination of pirfenidone with mycophenolate compared to mycophenolate alone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low to Very low**

Due to the lack of direct evidence for PICO 45, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 39 (pirfenidone vs no pirfenidone as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Moderate for PICO 25 and Low for PICO 39. An additional downgrade due to indirect comparison for PICO 45 resulted in a rating of Low (for mycophenolate) to Very low (for pirfenidone).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.

- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 39: direct evidence from 3 RCTs

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition,

hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.

- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 39.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 39

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270

3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3

PICO 46: In rheumatic disease patients with ILD, what is the impact of methotrexate compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 46, we provide indirect evidence from PICO 28 (methotrexate vs no methotrexate as first line ILD treatment) and PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 28 and Low for PICO 25. An additional downgrade due to indirect comparison for PICO 46 resulted in a rating of Very Low (for mycophenolate) and Very low (for methotrexate).

Key Findings from PICO 28: indirect evidence from 3 observational studies

- 3 observational studies of 381 RA-ILD patients reported that 60 (30.6%) patients classified as "progressive," and 71 (38.3%) patients classified as "stable" were taking methotrexate.
- 1 observational study reported that treatment with MTX, LEF, and tacrolimus were not associated with the progression of RA-ILD.
- 1 observational study reported that treatment with MTX was not associated with better survival (HR 0.58, 95% CI: 0.33 to 1.01).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.

- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5

deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 28 and PICO 25.

Table 46-1. PICO 46: Excluded Studies

References	Reasons for exclusion
Tille-Leblond et al. 2008[1]	No intervention of interest
Fu et al. 2019[2]	Wrong study design
Chen et al. 2022[3]	Wrong study design
Zamora-Legoff et al. 2016[4]	No intervention of interest

References for PICO 46

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.
2. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116.
3. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9.

References for Included Studies for PICO 28

1. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
2. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004

3. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

PICO 47: In rheumatic disease patients with ILD, what is the impact of leflunomide compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 47, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 27 (leflunomide vs no leflunomide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very Low for PICO 27. An additional downgrade due to indirect comparison for PICO 47 resulted in a rating of Very low (for mycophenolate) to Very low (for leflunomide).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.

- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 27: direct evidence from 2 observational studies:

- One single-center retrospective cohort study assessed the risk of infection of patients receiving methotrexate/leflunomide (n=54) vs. no therapy (n=48). The infection rate in the MTX/LEF group vs. no therapy group was 7.4 vs. 6.6 per 100 person-year (py), respectively.
- A multicenter prospective observational cohort study of RA-ILD patients exposed to either LEF, MTX, or TAC demonstrated that LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, p=0.031 and an

increased risk of ILD progression in patients with decreased lung function (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression and were at higher risk for ILD progression.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 27.

Table 47-1. PICO 47: Excluded Studies

References	Reasons for exclusion
Chen et al. 2022[1]	Wrong study design
Zamora-Legoff et al. 2016[2]	No intervention of interest

References for PICO 47

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 27

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
2. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

PICO 48: In rheumatic disease patients with ILD, what is the impact of azathioprine compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- One retrospective study (Oldham et al., 2016[1]) evaluated a composite endpoint of death, transplant, and respiratory hospitalizations in persons with fibrotic CT-ILD receiving either MMF or AZA. Events were counted per month of exposure. This study demonstrated very low-quality evidence of no statistically significant difference in the rate of events between the two groups (RR 1.18, 95% CI: 0.62 to 2.26); however, the number of events was small (1.5% [22/1,445] in the AZA group and 1.3% [16/1,237] in the MMF group). A subgroup analysis of patients with a UIP pattern on HRCT also showed no statistically significant difference between the groups (OR 0.87 (0.31 to 2.41); 1.1% [8/715] in AZA and 1.3% [7/545] in MMF).
- A second study—a case-control study—studied subjects with RA-ILD (Kelly et al., 2021[2]) and evaluated the relative risk of death in subjects who had received MMF or AZA compared to their RA no ILD indexed case controls so this analysis was an indirect comparison. In this study, RA-ILD subjects who received MMF (N=42) showed no difference in the rate of death (RR 0.65, 95% CI: 0.2 to 2.0) for all-cause mortality and (RR 1.7, 95% CI: 0.5 to 6.0) for respiratory mortality compared with their RA no ILD case controls. However, RA-ILD subjects who received AZA (N=54) had no similar risk for all-cause mortality (RR 1.42; 95% CI: 0.7 to 2.8) but had a higher risk for respiratory mortality; however, the number of events was very small (RR of 2.9; 95% CI: 1.2 to 6.9).
    - This might suggest that relative to AZA, MMF could be associated with lower mortality in subjects with RA-ILD. Notably, the subjects with RA-ILD who received MMF had a similar risk of death compared to their RA no ILD controls because overall the study found that patients with RA-ILD had a worse outcome than did those with RA without ILD (RA ILD, N=240 RR all-cause mortality 1.55 [95% CI: 1.01 to 2.4], RR of respiratory mortality 1.90 [95% CI: 0.9 to 3.9] compared with matched RA on ILD controls).
- Three retrospective studies studied pulmonary function test outcomes in subjects with CT- ILD.
    - One study (Oldham et al., 2016[1]) studied changes in % predicted FVC and % predicted DLco yearly in those receiving AZA vs. MMF for fibrotic CT-ILD. The mean difference for the % predicted FVC was 1.98 higher for AZA (95% CI: 0.36 to 3.6; 1.5 mean [SD 4.9]) for AZA vs. -0.5 mean [SD 3.2] for MMF). The mean difference for the % predicted

DLco was 6.50 higher for AZA (95% CI: 2.55 to 10.45; 4.5 mean [SD 11.9] for AZA vs. -2.0 mean [SD 7.8] for MMF).

- The second study researched the change in % predicted FVC and change in % predicted DLco at 24 months of follow-up in patients with myositis associated ILD (Huapaya et al., 2019[3]) and has similar results with the mean difference for % predicted FVC being 0.3 higher for AZA (95% CI: 0.59 to 1.19) and mean difference % predicted for DLco being 6 higher for AZA (95% CI: 4.88 to 7.12).
- The third study evaluated the change in % predicted FVC and % predicted DLco at 12 months after treatment with either AZA, MMF or RTXN in N=212 patients with RA ILD seen at 5 ILD centers in the US. Patients served as their own control with the comparator being estimated/imputed % predicted FVC and % predicted DLco based on PFTs performed in the 24 months prior to initiation of immunosuppression (Matson et al, 2023[4]). The mean difference in % predicted FVC for the entire group was +3.9%, 95% CI, 1.9-5.84 and the mean difference in % predicted DLco +4.53%, 95% CI 2.12-6.94. For the N=92 subjects who received AZA the mean difference in % predicted FVC was +3.48%, p=.07, and the mean difference in % predicted DLco was +1.93%, p=0.457. For the N=77 who received MMF, the mean difference in % predicted FVC was +4.55%, p=.002, and the mean difference in % predicted DLco +3.67%, p=.065. When comparing AZA to MMF, no difference was found in either change in % predicted FVC% or % predicted DLco% (FVC% predicted AZA:MMF p=0.787, DLCO % predicted AZA:MMF p=.59).

- Three retrospective studies explored the risk of AEs in patients receiving AZA vs. MMF (Oldham et al., 2016[1], Huapaya et al., 2019,[3] Matson et al., 2023[4]) For individual side effects, the number of events was very small, and while the ORs were overall lower for those receiving MMF, the CI did not indicate statistical significance in all cases but for a lower risk of transaminitis (absolute risk difference ranged from 78 fewer to 30 fewer patients with transaminitis in the MMF group; very low certainty of evidence).

Summary:

The overall body of evidence addressing this PICO question is very small. We included 4 retrospective studies due to the lack of any randomized or other prospective controlled studies. The quality of the studies is poor as they lack randomized allocation, thereby introducing very serious bias, and the outcomes were based on available data rather than high-quality ascertainment methods. Furthermore, each study included a different specific group of connective tissue (CT) associated interstitial lung disease (ILD), and thus the findings may not be comparable or widely applicable. Two of these studies were small and underpowered for the outcomes of interest (Oldham et al., 2016,[1] N=97, and Huapaya et al., 2019,[3] N=110); however, two studies (Kelly and Matson) included a higher

number of participants and were multicentered (Kelly et al., 2021,[2] N=290 RA-ILD and 290 RA-no ILD controls, Matson et al, 2023,[4] N=212 RA-ILD). However, study quality is poor to answer this PICO question, and the certainty of the evidence is very low.

The results of these studies do not allow us to draw any conclusions regarding the superiority of either MMF or AZA in treating CT-associated ILD with respect to either physiologic outcomes or mortality. They do underscore the need for a prospective study to answer this question.

Table 48-1. Retrospective Studies that do not provide data that allow quantitatively summarized

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results				
Kelly et al., 2021[2]	Rheumatoid arthritis-related interstitial lung disease – improving outcomes over 25 years: a large multicenter UK study Rheumatology Vol 60 Iss 4 Pgs 1882-1890	High. Retrospective but large, non ILD case controls, while the subjects who received MMF and AZA were similar in all important features (age, gender, disease duration, CT subtype and extent, smoking, serology and PFTs) those who received CYC were more likely to have UIP and to have more extensive disease limiting thus comparison between MMF and CYC is likely flawed.	25 years data related to CYC and MMF was only 13 years	N=240 pts with RA-ILD of whom 103 received with MMF (N=42), AZA (N=54) or CYC (N=21) followed by MMF (9) or AZA (9).	Compared with N=240 RA controls without ILD of whom 47 received AZA, MMF or CYC (specifics not given). These were case-matched controls who were matched for age (within 2 years), sex and date of RA diagnosis on a case-control basis with the index cases.	Group	#	All cause mort RR	Resp. mort. RR	p
						RA controls	**240**	**1.0**	**1.0**	
						IS rxt	47	1.36 (0.6-4.1)	1.48 (0.7-3.2)	0.46
						RA ILD	240	1.55 (1.01-2.4)	1.90 (0.9-3.9)	0.05
						RA ILD IS rxt	103	1.17 (0.7-2.1)	2.49 (1.1-5.6)	0.59
						AZA	**54**	**1.42 (0.7-2.8)**	**2.9 (1.2-6.9)**	**0.02**
						MMF	**42**	**0.65 (0.2-2.0)**	**1.7 (0.5-6.0)**	**0.36**
						CYC	21	1.65 (0.7-3.8)	3.6 (1.2-9.4)	0.02

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Matson et al., 2023[4]	Treatment Outcomes for Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Real-World, Multisite Study of the Impact of Immunosuppression on Pulmonary Function Trajectory Chest Vol Issue Pgs 1/23/23	High. All potential biases in retrospective studies: selection of immunosuppressive regimen was not random, dose was not uniform, outcome measures were not performed on a schedule and there were significant missing data points. Importantly, enrollment between immunosuppressive agents varied from center to center, for example, Baylor (N=30) prescribed MMF in 83.2% of its cohort vs only 13.3% prescribed AZA. The contrasts with Mayo (N=70) where 2.9% were prescribed MMF	Data was collected at 12 mos post treatment initiation	RA-ILD, N=212, AZA N=92, MMF N=77, RTXN N=43), overall 62.3% female with a mean age of 63.5 at treatment initiation. In the AZA group 57.7 were female, and mean age was 60.9. In the MMF group 74% were female and the mean age was 65.9.	Controls: pts served as their own controls with FVC and DLco % predicted untreated estimated by the slope of the PFTs pretreatment looking at the FVC % predicted and the DLco % predicted in the 24 mos pretreatment.	Group # FVC%pred Delta*, 95% CI DLco%pred Delta*, 95% CI p **RA ILD :all 212 +3.9% 1.9-5.84 +4.53% 2.12-6.94** AZA 92 +3.48 p=.07 1.93 p=.457 MMF 77 + 4.55 p=.002 +3.67 p=.065 *observed vs predicted based on pretreatment FVC or DLco Comparing AZA:MMF FVC%pred AZA:MMF p=0.787 DLCO%pred AZA:MMF p=0.595 See Table 48-4 for adverse events.

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
		vs 62.9 receiving AZA. Thus site difference in practice may also have led to unrecognized biases. The comparator relied on prediction based on a prior PFTs trend however only 95/212 patients had more that 1 PFT pre initiation of immunosuppression (sensitivity analysis including only these 95 pts demonstrated a similar finding with respect to the FVC and DLco as % predicted as was seen in the entire cohort). Also, it is important to note that only 38% of patients had a probable or definite UIP pattern based on a high resolution				

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
		chest CT scan. This is lower than is reported in the literature and thus suggests selection bias in whom to treat with immunosuppression. This may reflect either concern regarding the treatment of UIP with immunosuppression based on trials in idiopathic pulmonary fibrosis (specifically the Panther trial) or it may reflect a bias not to offer this patient immunosuppression due to a suspected lack of response. Interestingly, in a subset analysis, subjects with a UIP pattern had a similar response to immunosuppressi				

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
		on as those with a non-UIP pattern. Other limitations to the study included uncontrolled use of steroids and other DMARDs. The steroid use was similar between patients receiving AZA, MMF and RTXN.				

CYC: cyclophosphamide, MMF: mycophenolate mofetil, AZA: azathioprine, UIP: usual interstitial pneumonia, ILD: interstitial lung disease, RA: rheumatoid arthritis, IS: immunosuppressive, rxt: therapy, mort: mortality, resp: respiratory, CT: connective tissue

Table 48-2:PICO 48. AZA compared to MMF for CT associated fibrotic ILD: Composite and PFT Outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZA	MMF	Relative (95% CI)	Absolute (95% CI)		
Composite endpoint death, transplant, resp hospitalizations all patients (assessed with: The number of events/total months of exposure)												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	22/1445 (1.5%) [c]	16/1237 (1.3%) [c]	**OR 1.18** (0.62 to 2.26)	**2 more per 1,000** (from 5 fewer to 16 more)	⊕◯◯◯ Very low	CRITICAL
Composite Endpt death, transpt, resp hosp in UIP patt, mos exp (assessed with: Number of events/months of exposure)												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	8/715 (1.1%) [c]	7/545 (1.3%)	**OR 0.87** (0.31 to 2.41)	**2 fewer per 1,000** (from 9 fewer to 18 more)	⊕◯◯◯ Very low	CRITICAL
Change in % predicted FVC yearly-adj												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	serious[d]	serious[b]	none	54	43	-	MD **1.98 higher** (0.36 higher to 3.6 higher)	⊕◯◯◯ Very low	IMPORTANT
Change in % predicted FVC yearly-unadjusted												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	serious[d]	serious[b]	none	41	32	-	MD **2.09 higher** (0.48 higher to 3.7 higher)	⊕◯◯◯ Very low	IMPORTANT
Change in % predicted DLco yearly unadjusted												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	serious[d]	serious[b]	none	41	32	-	MD **7.01 higher** (2.93 higher to 11.09 higher)	⊕◯◯◯ Very low	IMPORTANT
Change in % predicted DLco yearly adj												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	serious[d]	serious[b]	none	54	43	-	MD **6.5 higher** (2.55 higher to 10.45 higher)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Retrospective study, concomitant meds were permitted, and steroid dose was different between the two groups at baseline as were the baseline FVC measures.

b. Very wide CI

c. These are the total months of exposure
d. Surrogate outcome

Table 48-3: AZA compared to MMF in Myositis Associated ILD: PFTs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZA	MMF	Relative (95% CI)	Absolute (95% CI)		
Change in % predicted FVC at 24 months-unadj												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious[b]	serious[d]	serious[c]	none	66	44	-	MD **0.3 higher** (0.59 lower to 1.19 higher)	⨁◯◯◯ Very low	IMPORTANT
Change in % Predicted DLco at 24 months-unadj												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious[b]	serious[d]	serious[c]	none	66	44	-	MD **6 higher** (4.88 higher to 7.12 higher)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. Retrospective data collection so no random assignment to groups. Some patients switched from one medication to another, and no other concomitant medications were allowed other than prednisone, but both prednisone dose and BL FVC were not balanced between groups. If pts switched, data collection for one medication was completed at that time, and the patient was then entered into the other arm for additional data collection.
b. While the data is presented in a different format than the Oldham study, the results are similar
c. Wide Confidence Intervals
d. Surrogate outcome

Table 48-4: PICO 48.MMF compared to AZA in CT-associated ILD: adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	AZA	Relative (95% CI)	Absolute (95% CI)		
Transaminitis												
Matson et al., 2023,[4] Oldham et al., 2016,[1] Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	not serious[b]	none	1/164 (0.6%)	17/212 (8.0%)	**OR 0.14** (0.03 to 0.61)	**68 fewer per 1,000** (from 78 fewer to 30 fewer)	⊕◯◯◯ Very low	CRITICAL
Nausea												
Oldham et al., 2016,[1] Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	1/87 (1.1%)	4/120 (3.3%)	**OR 0.54** (0.07 to 4.15)	**18 fewer per 1,000** (from 31 fewer to 92more)	⊕◯◯◯ Very low	CRITICAL
Pancytopenia												
Matson et al., 2023,[4] Oldham et al., 2016,[1] Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	4/164 (2.4%)	6/212 (2.8%)	**OR 0.88** (0.24 to 3.23)	3 fewer per 1,000 (from 21 fewer to 58 more)	⊕◯◯◯ Very low	CRITICAL
Pneumonia												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	0/44 (0.0%)	1/66 (1.5%)	**OR 0.49** (0.02 to 12.32)	**8 fewer per 1,000** (from 15 fewer to 144 more)	⊕◯◯◯ Very low	CRITICAL
Rash												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	very serious[b]	none	0/44 (0.0%)	1/66 (1.5%)	**OR 0.49** (0.02 to 12.32)	**8 fewer per 1,000** (from 15 fewer to 144 more)	⊕◯◯◯ Very low	CRITICAL
Abdominal Pain												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	very serious[b]	none	1/44 (2.3%)	0/66 (0.0%)	**OR 4.59** (0.18 to 115.17)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Diarrhea												
Huapaya et al., 2019[3]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	0/44 (0.0%)	2/66 (3.0%)	**OR 0.29** (0.01 to 6.18)	**21 fewer per 1,000** (from 30 fewer to 132 more)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF	AZA	Relative (95% CI)	Absolute (95% CI)		
Pancreatitis												
Oldham et al., 2016,[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	0/43 (0.0%)	1/54 (1.9%)	**OR 0.41** (0.02 to 10.32)	**11 fewer per 1,000** (from 18 fewer to 144 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Adverse Events not systematically collected based on retrospective nature of study
b. Wide Confidence Intervals
c.

Table 48-5. PICO 48: Excluded Studies

References	Reasons for exclusion
Amlani et al., 2020[5]	Wrong study design
Adler et al., 2018[6]	Wrong study design
Owen et al., 2016[7]	Wrong study design
Iudici et al., 2015[8]	Wrong study design
Okamoto et al., 2016[9]	Not a comparator of interest
Tillie-Leblond et al., 2008[10]	Not a comparator of interest
Grau et al., 1996[11]	Not a comparator of interest
Friedman et al., 1996[12]	Not a comparator of interest

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PICO 49: In rheumatic disease patients with ILD, what is the impact of cyclophosphamide compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one RCT (Scleroderma Lung Study II [SLS II])[1,2] suggested no difference in the risk of all-cause mortality, SSc-related mortality, and time to death among those in the CYC and MMF groups at follow-up up to 2 years; however, the study was not powered to detect mortality differences (low quality of evidence).
- Evidence from one RCT (SLS II) suggested no difference in the number of individuals meeting minimum clinically important difference (MCID) for quality of life at 12 and 24 months of follow-up (low quality of evidence).[3]
- Evidence from one RCT (SLS II) suggested no difference in the number of individuals meeting MCID for disability at 12 and 24 months of follow-up (low quality of evidence).[3]
- Evidence from the SLS II trial suggested no difference between the groups for Transitional Dyspnea Index and St. George's Respiratory Questionnaire (SGRQ) (among individuals who met or exceeded minimal clinically important difference) at 12 and 24 months of follow-up (low quality of evidence).[1]
- Harms:
    a. Evidence from the SLS II trial suggested a lower risk of leukopenia among individuals in the MMF group—4/69 (5.8%), compared to those in the CYC group—31/83 (37.3%). The absolute difference was 352 fewer individuals with leukopenia per 1,000 patients (95% CI: 390 fewer to 252 fewer) (low quality of evidence).[1]
    b. Evidence from two observational studies suggested a lower risk of lower respiratory tract infection among individuals in the MMF group—5/44 (11.4%), compared to those in the CYC group—10/33 (30.3%).[4,5] The absolute difference was 198 fewer cases per 1,000 (95% CI: 269 fewer to 17 fewer) (very low quality of evidence).
    c. Evidence from the SLS II trial and one observational study suggested no difference between CYC and MMF and the risk of anemia, hematuria, pneumonia, thrombocytopenia, rate of serious adverse events, rate of the treatment-related composite outcome at any follow-up (low quality of evidence).[1,4]

Summary:

Included was 1 RCT—SLS II—with four publications[1,3,6,7] which examined: changes in cough frequency,[6] high-resolution chest CT parameters,[7] and patient-related outcomes.[1,3]

Also included were 2 retrospective studies of patients with SSc ILD who had received either MMF or CYC with physiologic outcomes and 1 study that examined longer-term mortality in subjects enrolled in SLS I and SLS II.[2,4,5] The last included study was a large retrospective study of patients with rheumatoid arthritis (RA) that examined several immunosuppressive medications in patients with RA-ILD, including both CYC and MMF.[8]

One of the retrospective studies was a case-control analysis with only 10 subjects per treatment arm (MMF and CYC) and 6 patients in the control arm and had important baseline differences between subjects who received CYC vs. MMF.[4] The second retrospective study included 23 patients who received CYC compared with 34 patients who received MMF.[5] The evidence quality from these studies was very low, based largely on the high risk of bias and imprecision.

While the SLS II was a randomized controlled trial, the study was modest, with only 51 subjects in the CYC arm and 53 in the MMF arm. In addition, some analyses did not account for high attrition.[1]

While the RA-ILD study was a large study of 290 patients, MMF was used as a single agent; 18 of 21 patients who received CYC also received either MMF or AZA. Thus, this comparison was not used to support PICO 49.

Mortality

The SLS II trial suggested no difference in the risk of all-cause mortality, SSc-related mortality, and time to death at follow-up up to 2 years; however, the study was not powered to detect mortality differences (Table 49-1). For example, the risk of all-cause mortality in the SLS II study was estimated at OR 0.91; (95% CI: 0.40 to 2.03) and SSc-related mortality at OR 1.24 (95% CI: 0.42 to 3.61).[2]

Quality of Life and Disability

The SLS II trial estimated the difference in the number of individuals meeting the MCID for quality of life (≥5 at Short Form 36 (SF-36)) and disability (≤−0.14 at Health Assessment Questionnaire Disability Index (HAQ-DI)) at 12 and 24 months of follow-up (Table 2).[3] This study demonstrated no difference in the number of patients who met MCID for quality of life and disability between the CYC and MMF groups. For example, 18/53 (34.0%) individuals in the CYC arm and 18/53 (34.0%) in the MMF arm met MCID for the physical component of the SF-36 quality of life questionnaire at 24 months of follow-up (Table 49-2).

Harms

However, all three studies demonstrated increased risks associated with CYC.[1,4,5] Specifically, individuals randomized to CYC had a higher risk of leukopenia in the RCT (OR 0.09, [95% CI: 0.03 to 0.27; absolute risk reduction with MMF was 352 events fewer per 1,000 individuals [95% CI: 390 fewer to 252 fewer]; Table 49-3). The use of CYC was also associated with a higher risk of lower respiratory tract infections in two observational studies, compared to individuals taking MMF (OR 0.27 [95% CI: 0.08, 0.92], I^2=0%, n=77, 198 absolute risk reduction was 198 fewer infection incidence per 1,000 individuals [95% CI: 269 fewer to 17 fewer]). The SLS II study demonstrated no significant differences between interventions concerning pneumonia (OR 1.35 [95% CI: 0.35, 5.24]), hematuria (OR 1.61 [95% CI: 0.26, 9.96]), thrombocytopenia (OR 0.11 [95% CI: 0.01, 2.10]), or neutropenia (OR 0.43 [95% CI: 0.11, 1.73]); however, the event rate was very low. The risk of organ failure did not differ between the groups (OR 0.92, 95% CI: 0.31 to 2.68; Table 49-5). The rate of serious adverse events (SAEs; Table 49-4) in SLS I was similarly not significantly different between the groups concerning the number of subjects experiencing SAEs, total SAE events, or disease-related SAEs. Observational studies demonstrated the same effect direction as the RCT.

Transitional Dyspnea Index and St. George's Respiratory Questionnaire

The SLS II trial found no difference between the groups for Transitional Dyspnea Index (TDI) and SGRQ (the number of individuals who met or exceeded MCID of ≥1 for TDI and ≤−4.0 for SGRQ) at 12 to 24 months of follow-up (Table 49-2).[1,3] Individuals in both groups improved at the same rate.

Treatment Failure

Treatment failure (defined as an absolute decrease from baseline FVC of ≥15% of predicted occurring ≥3 months after randomization and lasting for ≥1 month) rate was assessed, although the number of events was very small—2 (2.7%) in the CYC group and 0 in the MMF group (Table 49-8). Therefore, this event rate does not allow a conclusion about the differential effects of CYC and MMF.

Disease Progression: Forced Vital Capacity (FVC), Diffusion Capacity for Carbon Monoxide (DLCO), Total Lung Capacity

In SLS II (n=126), the CYC group was treated with CYC (target dose 2·0 mg/kg/day) for 1 year, followed by a placebo for another year. The MMF group received treatment with MMF (target dose 1500 mg twice daily) for 2 years.[1] In the case-control study (n=20; Panopoulos et al., 2016[4]), patients were enrolled either upon diagnosis of ILD or as a primary treatment after a decline in FVC of >10% over the previous 12 months. Duration of treatment varied but included an FVC at 12 and 24 months of follow-up.

The SLS II demonstrated that CYC was associated with a greater reduction of % pred. DLco, compared with MMF at 12 months of follow-up (Table 49-6). Thus, the mean difference between the groups was -4.99 (95% CI: -7.67, -2.31). The Panopoulos et al., 2013[4] case-control study displayed a tendency to favor MMF with a mean difference of 4.90 (95% CI: -4.83, 14.63); however, the difference was not statistically significant. There was no statistically significant difference between the groups for % pred. FVC in either study at 12 months of follow-up (-0.21 [95% CI: -2.26 to 1.84] in SLS II; 1.20 [95% CI: -5.99 to 8.39] in Panopoulos et al., 2013[4]). None of the single studies demonstrated a statistically significant difference in FVC and DLco between the groups at 24 months of follow-up. The pooled data from both studies (SLS II and Panopoulos et al., 2013[4]) also showed no difference in either of the primary outcomes, change in % predicted FVC and DLco at 24 months of follow-up. The mean difference between arms was 0.80 (95% CI: -1.46 to 3.06) for the % pred. FVC and 2.66 (95% CI: -8.02, 13.33) for % pred. DLco (Table 49-6).

The studies also looked at 6 months of follow-up (Table 49-6). The data from the 6-month analysis included patients from the second retrospective study Shenoy et al., 2016[5] in addition to SLS II and also did not demonstrate any significant difference in % FVC between groups at 6 months (MD 4.3 [95% CI: -2.48, 11.34] and -1.26 [95% CI: -3.32, 0.80], respectively).[1]

There was no difference in total lung capacity (TLC) in either intervention group at any follow-up in the RCT and one observation study (Table 49-6). For example, the SLS II trial demonstrated a % pred. TLC mean difference of -0.19 (95% CI: -2.28 to 1.89) at 12 months and -0.80 (95% CI: -34.2 to 1.84) at 24 months of follow-up.

Disease Progression: High-Resolution Chest CT, Skin Thickness

High-Resolution Chest CT:

Both the original SLS II publication and its ancillary analysis (Kim et al., 2020[7]) studied changes in high-resolution chest CT (HRCT) scanning's quantitative lung fibrosis (QLF) scores. At 24 months of follow-up, the SLS II study demonstrated no between-group differences in fibrosis in the lung most involved (QLF-LM) or the whole lung (QLF-WL) (Table 49-7).[1] There was no statistically significant difference in the HRCT quantitative interstitial lung disease (QILD) score in the lobe of maximal involvement (QILD-LM). Kim et al., 2020[7] examined the transition probability among normal lung, ground glass opacities (GGO), or lung fibrosis. There was no significant difference in the transitional probabilities between treatment arms ($p=0.52$ for the whole lung and $p=0.47$ for the most severely affected lobe). However, both arms showed a net reduction in the amount of GGO to normal lung (p-values of <0.001) for both the whole lung and the most severe lobe. Both arms also showed a net reduction in lung fibrosis to the normal lung for the whole lung ($p<0.001$) and for the most severe lobe ($p<0.05$). However, neither arm showed a net reduction in lung fibrosis to GGO for the whole lung or most severe lobe.

Skin Thickness:

Subjects from both groups in the SLS II trial improved the mRSS. However, there was no statistically significant difference between groups at 2 years of follow-up (MD 0.11 higher; 95% CI: 2.72 lower to 2.94 higher) (Table 49-9).

Table 49-1: CYC vs. MMF in SSc ILD: Mortality SLS II be used for CT-ILD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF in SSc ILD: Mortality SLS II	Relative (95% CI)	Absolute (95% CI)		
Mortality SLS II												
Tashkin et al., 2016[1]	randomised trials	serious[a]	not serious	not serious	serious[b,d]	none	11/69 (15.1%)	5/69 (7.2%)	**OR 2.27** (0.75 to 6.91)	**78 more per 1,000** (from 17 fewer to 278 more)	⊕⊕◯◯ Low	CRITICAL
Short term SSc related mortality in follow-up to SLS II												
Volkmann et al., 2019[2*]	randomised trials	serious[c]	not serious	not serious	Serious[b,d]	none	7/73 (9.6%)	8/69 (11.6%)	**OR 1.24** (0.42 to 3.61)	**24 more per 1,000** (from 64 fewer to 205 more)	⊕⊕◯◯ Low	CRITICAL
Short term all-cause mortality in SSc ILD follow-up SLS II												
Volkmann et al., 2019[2*]	randomised trials	serious[c]	not serious	not serious	Serious[b,d]	none	16/73 (21.9%)	14/69 (20.3%)	**OR 0.91** (0.40 to 2.03)	**15 fewer per 1,000** (from 110 fewer to 138 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

*This is a follow-up study to SLS II looking at longer-term mortality. Survival status could not be determined in 12 participants. The median follow-up time for all patients in SLS II was 3.6 years. This study breaks mortality down into SSc related and all-cause. While they looked at both SLS I and SLS II, only the data from SLS II is included here, so this adds some additional longer-term mortality to the original mortality data from SLS I with a longer f/u, so the original SLS II paper cases are also included here for a longer f/u.

Explanations

- **a.** One death deemed probably due to underlying SSc and not the treatment. Three of the deaths occurred while subjects were still on the study drug; the remainder occurred 1–17 months after patients had withdrawn from treatment.
- **b.** RCT but small trial size.
- **c.** Given ~10% of patients had an unknown survival status at the follow-up point, this could have resulted in bias if these unknowns were not evenly distributed between groups. 10% were in the CYC arm and 6% in the MMF arm.
- **d.** Wide confidence intervals

Table 49-2. CYC compared to MMF for SSc-ILD, Patient-Reported Outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Change in TDI 24 months: secondary outcome prim. analysis												
Tashkin et al., 2016[1*]	randomised trial	very serious[b]	not serious	not serious	serious[a]	none	39	40	-	MD **0.39 higher** (1.01 lower to 1.79 higher)	⊕◯◯◯ Very Low	CRITICAL
# of patients who met or exceeded MCID TDI at 24 mos												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	serious[a]	none	23/39 (59.0%)	19/40 (47.5%)	**OR 1.59** (0.65 to 3.87)	**115 more per 1,000** (from 105 fewer to 303 more)	⊕⊕◯◯ Low	CRITICAL
# of pts. who met or exceeded MCID SGRQ at 12 months (St Georges Resp Ques)												
Volkman n et al., 2020[3*]	randomised trials	serious	not serious	not serious	serious[a]	none	31/55 (56.4%)	28/57 (49.1%)	**OR 1.34** (0.64 to 2.82)	**73 more per 1,000** (from 109 fewer to 240 more)	⊕⊕◯◯ Low	CRITICAL
# of pts. who met or exceeded MCID for SCRG at 24 mos												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	serious[a]	none	29/53 (54.7%)	25/52 (48.1%)	**OR 1.30** (0.61 to 2.81)	**65 more per 1,000** (from 120 fewer to 242 more)	⊕⊕◯◯ Low	CRITICAL
# of pt who met or exceeded MCID TDI at 12 mos												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	serious[a]	none	21/45 (46.7%)	19/49 (38.8%)	**OR 1.38** (0.61 to 3.14)	**79 more per 1,000** (from 109 fewer to 278 more)	⊕⊕◯◯ Low	CRITICAL
Quality of Life-Mental Component Summary (Short Form 36 [SF-36]) - 12 month of follow-up (# of patients who met or exceeded MCID)												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	serious[a]	none	23/53 (43.4%)	22/53 (41.5%)	**OR 1.08** (0.50 to 2.33)	**19 more per 1,000** (from 153 fewer to 208 more)	⊕⊕◯◯ Low	CRITICAL
Quality of Life-Mental Component Summary (Short Form 36 [SF-36]) - 24 months of follow-up (# of patients who met or exceeded MCID)												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	seriousa	none	21/53 (39.6%)	22/53 (41.5%)	**OR 0.92** (0.43 to 2.01)	**20 fewer per 1,000** (from 181 fewer to 173 more)	⊕⊕◯◯ Low	CRITICAL
Quality of Life-Physical Component Summary (Short Form 36 [SF-36]) - 12 month of follow-up (# of patients who met or exceeded MCID)												
Volkman n et al., 2020[3*]	randomised trial	serious	not serious	not serious	serious[a]	none	19/53 (35.8%)	17/53 (32.1%)	**OR 1.18** (0.53 to 2.65)	**37 more per 1,000** (from 121 fewer to 235 more)	⊕⊕◯◯ Low	CRITICAL
Quality of Life-Physical Component Summary (Short Form 36 [SF-36]) - 24 months of follow-up (# of patients who met or exceeded MCID)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Volkman n et al., 2020[3*]	randomise d trial	serious	not serious	not serious	serious[a]	none	18/53 (34.0%)	18/53 (34.0%)	**OR 1.00** (0.45 to 2.23)	**0 fewer per 1,000** (from 152 fewer to 195 more)	⊕⊕◯◯ Low	CRITICAL
Disability-Health Assessment Questionnaire Disability Index (HAQ-DI) - 12 month of follow-up (# of patients who met or exceeded MCID)												
Volkman n et al., 2020[3*]	randomise d trial	serious	not serious	not serious	serious[a]	none	20/53 (37.7%)	15/53 (28.3%)	**OR 1.54** (0.68 to 3.47)	**95 more per 1,000** (from 71 fewer to 295 more)	⊕⊕◯◯ Low	CRITICAL
Disability-Health Assessment Questionnaire Disability Index (HAQ-DI) - 24 months of follow-up (# of patients who met or exceeded MCID)												
Volkman n et al., 2020[3*]	randomise d trial	serious	not serious	not serious	serious[a]	none	18/53 (34.0%)	15/69 (21.7%)	**OR 1.85** (0.83 to 4.15)	**122 more per 1,000** (from 30 fewer to 318 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MCID:** minimal clinically important difference; **MD:** mean difference; **OR:** odds ratio; **SGRQ:** St. George's Respiratory Questionnaire; **TDI:** Transitional Dyspnea Index

*This is a new data analysis from SLS II looking at the minimum clinically important difference.

Explanations

a. Small study size and wide CI

b. Almost one-half of the participants were excluded from the analysis

Table 49-3. MMF compared to CYC in SSc -ILD: Adverse Event Rate

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF in SSc ILD Adverse Events	CYC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Anemia												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a,]	randomised trial and case-control	serious[c]	not serious	not serious	serious[b]	none	8/79 (10.1%)	14/83 (16.9%)	**OR 0.57** (0.23 to 1.43)	**65 fewer per 1,000** (from 124 fewer to 56 more)	⊕◯◯◯ Very Low	CRITICAL
Anemia - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious	not serious	serious[b]	none	8/69 (11.6%)	13/73 (17.8%)	**OR 0.61** (0.23 to 1.57)	**61 fewer per 1,000** (from 131 fewer to 76 more)	⊕⊕◯◯ Low	CRITICAL
Anemia - Case-control												
Panopoulos et al., 2013[4]	case-control	serious[d]	not serious	not serious	very serious[b]	none	0/10 (0.0%)	1/10 (10.0%)	**OR 0.30** (0.01 to 8.33)	**68 fewer per 1,000** (from 99 fewer to 381 more)	⊕◯◯◯ Very Low	CRITICAL
Hematuria												
Tashkin et al., 2016[1,a]	randomised trials	serious	not serious	not serious	serious[b]	none	3/69 (4.3%)	2/73 (2.7%)	**OR 1.61** (0.26 to 9.96)	**16 more per 1,000** (from 20 fewer to 192 more)	⊕⊕◯◯ Low	CRITICAL
Leukopenia (persons with Leukopenia)												
2 Tashkin et al.,2016[1], Panopoulos et al., 2013[4,a,c]	randomised trial and case-control	serious[c]	not serious	not serious	serious[b]	none	4/79 (5.1%)	31/83 (37.3%)	**OR 0.10** (0.03 to 0.29)	**317 fewer per 1,000** (from 356 fewer to 226 fewer)	⊕⊕◯◯ Low	CRITICAL
Leukopenia (persons with Leukopenia) - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious	not serious	serious[b]	none	4/69 (5.8%)	30/73 (41.1%)	**OR 0.09** (0.03 to 0.27)	**352 fewer per 1,000** (from 390 fewer to 252 fewer)	⊕⊕◯◯ Low	CRITICAL
Leukopenia(persons with Leukopenia) - Case-control												
Panopoulos et al., 2013[4]	case-control	serious[c]	not serious	not serious	very serious[b]	none	0/10 (0.0%)	1/10 (10.0%)	**OR 0.30** (0.01 to 8.33)	**68 fewer per 1,000** (from 99 fewer to 381 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MMF in SSc ILD Adverse Events	CYC	Relative (95% CI)	Absolute (95% CI)		
Lower Resp Tract Infections												
2 Panopoulos et al., 2013[4], Shenoy et al., 2016[5,a,d]	observational studies	serious[c]	serious	not serious	serious[e]	none	5/44 (11.4%)	10/33 (30.3%)	**OR 0.27** (0.08 to 0.92)	**198 fewer per 1,000** (from 269 fewer to 17 fewer)	⊕◯◯◯ Very low	CRITICAL
Neutropenia												
Tashkin et al., 2016[1,a]	randomised trials	serious	not serious	not serious	serious[b]	none	3/69 (4.3%)	7/73 (9.6%)	**OR 0.43** (0.11 to 1.73)	**52 fewer per 1,000** (from 84 fewer to 59 more)	⊕⊕◯◯ Low	CRITICAL
Pneumonia												
Tashkin et al., 2016[1],[a]	randomised trials	serious	not serious	not serious	serious[b]	none	5/69 (7.2%)	4/73 (5.5%)	**OR 1.35** (0.35 to 5.24)	**18 more per 1,000** (from 35 fewer to 178 more)	⊕⊕◯◯ Low	CRITICAL
Thrombocytopenia												
Tashkin et al., 2016[1,a]	randomised trials	serious	not serious	not serious	serious[b]	none	0/69 (0.0%)	4/73 (5.5%)	**OR 0.11** (0.01 to 2.10)	**48 fewer per 1,000** (from 54 fewer to 54 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

- **a.** This outcome looks at the number of SUBJECTS who had Adverse Events (not the total number of events experienced- some subjects had an event more than once -so these would be counted twice for that subject if we were looking at EVENTS, here I only looked at SUBJECTS to be consistent between studies)
- **b.** Small study size
- **c.** One trial was an RCT, the other was a retrospective case-control which was very small.
- **d.** Both studies are retrospective. The smaller of the two (N=10/10) was a case-control study, the second was a cohort study, but treatment was via a protocol; however, patients selected the arm.
- **e.** One study had far more events reported than the other.

Table 49-4. CYC compared to MMF in SSc-ILD: Serious Adverse Events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Number of Subjects with SAE												
Tashkin et al., 2016[1,a,b]	randomised trials	serious	not serious	not serious	serious[c]	none	22/73 (30.1%)	27/69 (39.1%)	**OR 0.67** (0.33 to 1.35)	**90 fewer per 1,000** (from 216 fewer to 73 more)	⊕⊕◯◯ Low	CRITICAL
Total SAE events												
Tashkin et al., 2016[1,b]	randomised trials	serious	not serious	not serious	serious[c]	none	36/73 (49.3%)	42/69 (60.9%)	**OR 0.63** (0.32 to 1.22)	**114 fewer per 1,000** (from 276 fewer to 46 more)	⊕⊕◯◯ Low	CRITICAL
Treatment related SAEs												
Tashkin et al., 2016[1,b]	randomised trials	serious	not serious	not serious	serious[c]	none	8/73 (11.0%)	3/69 (4.4%)	**OR 2.71** (0.69 to 10.66)	**66 more per 1,000** (from 13 fewer to 283 more)	⊕⊕◯◯ Low	CRITICAL
Ds related SAEs												
Tashkin et al., 2016[1,b]	randomised trials	serious	not serious	not serious	very serious[c]	none	16/73 (21.9%)	16/69 (23.2%)	**OR 0.93** (0.42 to 2.04)	**13 fewer per 1,000** (from 119 fewer to 149 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio; **SAE**: serious adverse events

Explanations

a. This outcome looks at the number of SUBJECTS who had Serious Adverse Events (not the total number of events experienced- some subjects may have had an event more than once or had different SAEs-so these would be counted twice for that subjects when we look at total events)

b. This outcome looks at the number of EVENTS that occurred (not the number of subjects. Some subjects had an event more than once or had different SAEs-so these would be counted twice for that subjects when we look at total events)

c. Trial had a small number of patients

Table 49-5. CYC compared to MMF for SSC-ILD, Short-Term Organ System Failures

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Organ System Failures												
Volkman n et al., 2019[2,a]	randomise d trials	serious[b]	not serious	not serious	serious[c]	none	8/73 (11.0%)	7/68 (10.1%)	**OR 0.92** (0.31 to 2.68)	**7 fewer per 1,000** (from 68 fewer to 131 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Follow-up study to SLS II looking at short-term follow-up organ system failures follow-up was 3.6 years, and 12 patients lost to follow-up

b. The patients who were lost to follow-up may have differed from those who were available for follow-up data collection. IE maybe higher mortality due to organ failures which were more prevalent in one arm or the other.

c. Small number of patients in the study and wide confidence intervals.

Table 49-6. Change in % pred FVC BL, % pred Dlco, and Total Lung Capacity

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF in SSc ILD PFTs	Relative (95% CI)	Absolute (95% CI)		
Change in % pred FVC BL to 6 months												
2 Tashkin et al., 2016[1], Shenoy et al., 2016[5,c]	randomised trial and case-control	serious	not serious[c]	serious[d]	serious[b]	none	79	94	-	MD **0.59 higher** (4.63 lower to 5.81 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred FVC BL to 6 months - RCT												
Tashkin et al., 2016[1]	randomised trial	not serious	not serious	serious[d]	serious[b]	none	51	53	-	MD **1.26 lower** (3.32 lower to 0.8 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in % pred FVC BL to 6 months - Case-control												
Shenoy et al., 2016[5]	case-control	serious	not serious	serious[d]	serious[b]	none	23	34		MD **4.3 higher** (2.48 lower to 11.34 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in FVC % pred at 24 months: prim outcome, primary analysis												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trial and case-control	serious	not serious	serious[d]	serious[b]	none	61	63	-	MD **0.8 higher** (1.46 lower to 3.06 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in FVC % pred at 24 months: prim outcome, long jt model - RCT												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF in SSc ILD PFTs	Relative (95% CI)	Absolute (95% CI)		
Tashkin et al., 2016[1]	randomised trial	serious	not serious	serious[d]	serious[b]	none	51	53	-	MD **0.69 higher** (1.62 lower to 3 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in FVC % pred at 24 months: prim outcome, long jt model - case-control												
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very serious[b]	none	10	10	-	MD **3 higher** (7.44 lower to 13.44 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in FVC % pred at 24 months: prim outcome secondary analysis based on freq dist. (ad hoc)												
Tashkin et al., 2016[1]	randomised trial	serious	not serious	serious[d]	very serious[b]	none	51	53	-	MD **0.3 lower** (3.49 lower to 2.89 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred FVC at 12 mos												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trial and case-control	serious	not serious	serious[d]	serious[b]	none	61	69	-	MD **0.1 lower** (2.08 lower to 1.87 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred FVC at 12 months - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious	serious[d]	serious[b]	none	51	59	-	MD **0.21 lower** (2.26 lower to 1.84 higher)	⊕⊕◯◯ Low	IMPORTANT
Change in % pred FVC at 12 months - Case-control												
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very serious[b]	none	10	10	-	MD **1.2 higher** (5.99 lower to 8.39 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred DLco at 12 mos												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trial and case-control	serious	serious[c]	serious[d]	very serious[b]	none	66	68	-	MD **1.2 lower** (10.62 lower to 8.23 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred DLco at 12 months - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious[c]	serious[d]	serious[b]	none	56	58	-	MD **4.99 lower** (7.67 lower to 2.31 lower)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred DLco at 12 months - Case-control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF in SSc ILD PFTs	Relative (95% CI)	Absolute (95% CI)		
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very seriousb	none	10	10	-	MD **4.9 higher** (4.83 lower to 14.63 higher)	⊕◯◯◯ Very Low	IMPORTANT
% Change DLco BL to 24 mos												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trial and case-control	serious	not serious	serious[d]	very serious[b]	none	58	62	-	MD **2.66 higher** (8.02 lower to 13.33 higher)	⊕◯◯◯ Very Low	IMPORTANT
% Change DLco BL to 24 months - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious	serious[d]	serious	none	58	52	-	MD **1.74 lower** (5.09 lower to 1.61 higher)	⊕◯◯◯ Very Low	IMPORTANT
% Change DLco BL to 24 months - Case-control												
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very serious[b]	none	10	10	-	MD **9.4 higher** (1.17 lower to 19.97 higher)	⊕◯◯◯ Very Low	IMPORTANT
% pred change in TLC BL to 24 mos												
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trial and case-control	serious	not serious	serious[d]	serious[b]	none	61	63	-	MD **0.62 lower** (3.14 lower to 1.89 higher)	⊕◯◯◯ Very Low	IMPORTANT
% pred change in TLC BL to 24 months - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious[c]	serious[d]	serious[b]	none	51	53	-	MD **0.8 lower** (3.42 lower to 1.84 higher)	⊕◯◯◯ Very Low	IMPORTANT
% pred change in TLC BL to 24 months - Case-control												
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very serious[b]	none	10	10	-	MD **1.1 higher** (7.38 lower to 9.58 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred TLC BL to 12 mos												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF in SSc ILD PFTs	Relative (95% CI)	Absolute (95% CI)		
2 Tashkin et al., 2016[1], Panopoulos et al., 2013[4,a]	randomised trials	serious	not serious	serious[d]	serious[b]	none	64	67	-	MD **0.15 lower** (2.2 lower to 1.9 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred TLC BL to 12 months - RCT												
Tashkin et al., 2016[1]	randomised trial	serious	not serious[c]	serious[d]	serious[b]	none	54	57	-	MD **0.19 lower** (2.27 lower to 1.89 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in % pred TLC BL to 12 months - Case-control												
Panopoulos et al., 2013[4]	case-control	serious	not serious	serious[d]	very serious[b]	none	10	10	-	MD **1.1 higher** (10.66 lower to 12.86 higher)	⊕◯◯◯ Very Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **TLC**: total lung capacity

Explanations

a. One of the studies was a double-blind, randomized control trial (SLSII); however, the second study was a retrospective case-controlled study that was relatively small.

b. The RCT was small, and the confidence intervals were relatively wide; thus, there is some imprecision in the outcome.

c. One of the studies was a double-blind, randomized controlled trial (SLS II); however, the second study was a retrospective study, however modest in size, and patients were treated on the protocol. My assessment of certainty is based mostly on the data from the RCT, but these studies showed different outcomes at 6 months which should be pointed out. That would lead to a serious level of inconsistency, but one should be careful as selecting that may unfairly give too much weight to the retrospective study. Thus, we opted NOT to consider this inconsistent.

d. Surrogate outcomes

Table 49-7. CYC compared to MMF for SSc-ILD: HRCT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Change in HRCT QLF-LM (lung most involved)												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	51	-	MD **0.39 lower** (2.6 lower to 1.82 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in HRCT QLF-WL (whole lung)												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	51	-	MD **1.02 lower** (4.96 lower to 2.92 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in HRCT QILD-WL												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	51	-	MD **0.89 lower** (5.34 lower to 3.56 higher)	⊕◯◯◯ Very Low	IMPORTANT
Change in HRCT QILD-LM												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	51	-	MD **0.27 lower** (3.54 lower to 3 higher)	⊕◯◯◯ Very Low	IMPORTANT
Probability GG to NL less Probability NL to GG, Whole Lung												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.02 higher** (0.08 lower to 0.12 higher)	⊕◯◯◯ Very Low	IMPORTANT
Probability GG to NL less Probability NL to GG, Most severe lobe												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.03 higher** (0.08 lower to 0.14 higher)	⊕◯◯◯ Very Low	IMPORTANT
Probability LF to GGO less Probability GG to LF, Whole lung												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.05 higher** (0.04 lower to 0.13 higher)	⊕◯◯◯ Very Low	IMPORTANT
Probability LF to GGO less Probability GG to LF, Most severe lobe												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.06 higher** (0.05 lower to 0.17 higher)	⊕◯◯◯ Very Low	IMPORTANT
Prob of LF to NL less Probability of NL to LF, Whole Lung												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.02 higher** (0.04 lower to 0.08 higher)	⊕◯◯◯ Very Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Probability of LF to NL less Probability of NL to LF, most severe lobe												
Kim et al., 2020[7,b]	randomised trials	serious	not serious	serious[c]	serious[a]	none	47	50	-	MD **0.05 higher** (0.06 lower to 0.16 higher)	⨁◯◯◯ Very Low	IMPORTANT

CI: confidence interval; **GG:** ground glass; **HRCT:** high-resolution chest computed tomography; **LF**: lung fibrosis; **MD:** mean difference; **NL:** normal lung; **QLF-LM:** quantitative lung fibrosis lung most involved; **QLF-WL:** quantitative lung fibrosis whole lung

Explanations

a. Small trial size and wide CI

b. This is a follow-up study from SLS II

c. Surrogate outcomes

Table 49-8. CYC compared to MMF for SSc-ILD: Treatment Failure (drip of FVC > 15% after 3 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Treatment Failure												
Tashkin et al., 2016[1]	randomised trial	very serious[a]	not serious	serious[c]	very serious[a,b]	none	2/73 (2.7%)	0/69 (0.0%)	**OR 4.86** (0.23 to 103.06)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very Low	IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations

a. Small study size
b. Wide confidence interval
c. Surrogate outcomes

Table 49-9. CYC compared to MMF for SSc-ILD, mRSS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYC	MMF	Relative (95% CI)	Absolute (95% CI)		
Change in mRSS BL to 24 months sec outcome long jt model												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[b]	serious[a]	none	53	53	-	MD **0.45 lower** (2.56 lower to 1.66 higher)	⨁◯◯◯ Very Low	NOT IMPORTANT
change in mRSS BL to 24 months sec analysis												
Tashkin et al., 2016[1]	randomised trials	serious	not serious	serious[b]	serious[a]	none	55	58	-	MD **0.11 higher** (2.72 lower to 2.94 higher)	⨁◯◯◯ Very Low	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference; **mRSS**: modified Rodnan measurement method

Explanations

a. Relatively small trial and CI is wide

Table 49-10. Outcomes not entered into REVMAN/GRADEPRO

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Kelly et al., 2021[8]	Rheumatoid arthritis related interstitial lung disease – improving outcomes over 25 years: a large multicenter UK study	Retrospective but large, non ILD case controls, while the patients who received MMF and AZA were similar in all important features (age, gender, disease duration, CT subtype and extent, smoking, sero and PFTs) those who received CYC were more likely to have UIP and to have more extensive disease limiting thus comparison between MMF and CYC is likely flawed.	25 years although data related to CYC and MMF was only 13 years	N=240 patients with RA-ILD of whom 103 received with MMF (N=42), AZA (N=54) or CYC (N=21) followed by MMF (9) or AZA (9).	Compared with N=240 RA controls without ILD of whom 47 received AZA, MMF or CYC (specifics not given).	Group # all cause mort. RR resp. mort. p RR **RA controls 240 1.0 1.0** IS rxt 47 1.36 (0.6-4.1) 1.48 (0.7-3.2) 0.46 RA ILD 240 1.55 (1.01-2.4) 1.90 (0.9-3.9) 0.05 RA ILD IS rxt 103 1.17 (0.7-2.1) 2.49 (1.1-5.6) 0.59 AZA 54 1.42 (0.7-2.8) 2.9 (1.2-6.9) 0.02 **MMF 42 0.65 (0.2-2.0) 1.7 (0.5-6.0) 0.36** **CYC 21 1.65 (0.7-3.8) 3.6 (1.2-9.4) 0.02**
Tashkin et al., 2017[6]	Improved Cough and Cough-	**Note:** See *REVMAN under SLS II study 2996*	24 months	SSc-ILD, N=142 only 126 patients had data to allow	**CYC** up titrated to 1.8 to 2.3 mg/kg po daily x 12 months	<u>Cough at Baseline to Cough at 24 mos.</u> **CYC**: 44/73 (60.3%), to 24/53 (45.3%) dec 44% p<0.05 **MMF**: 43/68 (63.2%), to 24/52 (46.2) dec 41% p<0.05

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
	Specific Quality of Life in Patients Treated for Scleroderma-Related Interstitial Lung Disease Results of Scleroderma Lung Study II	*Also bias noted by authors was no placebo arm*		inclusion in analysis. N=63 MMF arm N=63 CYC arm Mean age 52 yrs. F 73.9% First SSc symptoms mean 2.6 years prior to enrollment 58.5 with dc Mean FVC 66.5 % predicted Mean TLC 65.8 % predicted Mean DLco 54 % predicted No difference in study arms with respect to baseline characteristics	followed by 12 months placebo vs **MMF** up titrated to a dose of 1.5 grams BID x 24 months	
Panopoulos et al., 2013[4]	Mycophenolate Versus	Retrospective case control study, small	12 and 24 mos.	SSc ILD	*Note:*	Mycophenolate p intra-group Cyclophosphamide p intra-group HRCT score (Warrick et al.)

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
	Cyclophosphamide for Progressive Interstitial Lung Disease Associated with Systemic Sclerosis: A 2-Year Case Control Study	(N=20, 10 per treatment arm) single center While baseline data noted to be similar, there was at least one significant difference: More patients got MMF for a dec in FVC than for a new dx. In addition, MMF patients had a longer ds duration			*1. PFT data entered into REVMAN* *2. HRCT data entered here given unique measurement techniques and small N did not enter into RevMan*	Baseline 10.0 ± 8.9 vs 14.5 ± 7.4 1st year 12.0 ± 8.3 vs 16.1 ± 6.5 2nd year 12.7 ± 8.2 vs 16.5 ± 5 Delta HRCT-score b-1* 2.0 ± 2.3 p 0.066 vs 1.6 ± 3.5 p=0.18 Delta HRCT-scoreb-2* 2.7 ± 3.0 p=0.039 vs 2.0 ± 4.0 p=0.197 HRCT score (Desai et al.) Coarseness baseline 5.1 ± 4.6 vs 8 ± 3.5 Coarseness 1st year 6.6 ± 5.0 vs 8.6 ± 3.4 Coarseness2nd year 6.9 ± 4.9 vs 9.3 ± 3.1 Dcoarsenessb-1* 1.5 ± 2.0 p=0.068 vs 0.6 ± 1.7 p=0.317 Dcoarsenessb-2* 1.8 ± 2.2 p=0.063 1.3 ± 1.8 p=0.18 Disease extent (%)baseline 21.7 ± 22.9 vs 28.8 ± 17.8 Disease extent (%)1st year 25.0 ± 23.1 vs 32.3 ± 17.9 Disease extent (%)2nd year 26.0 ± 22.9 vs 33.4 ± 17.4 delta extentb-1* 3.25 ± 2.7 p=0.034 3.5 ± 6.3 p=0.102 delta extentb-2* 4.25 ± 3.8 p=0.041 vs 4.6 ± 6.6 p=0.102

AZA: azathioprine; **CYC:** Cyclophosphamide; **dx:** diagnosis**; ILD:** interstitial lung disease; **MMF:** mycophenolate; **mort.:** mortality; **RA**: rheumatoid arthritis; **resp.:** respiratory; **UIP:** usual interstitial pneumonia; **mos:** months

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Table 49-11. PICO 49: Excluded Studies

References	Reasons for exclusion
Campos et al., 2011[1]	Not a comparator of interest
Kundu et al., 2016[2]	Not a comparator of interest
Li et al., 2019[3]	Population not of interest
Namas et al., 2018[4]	No outcome of interest
Bodolay et al., 2005[5]	Not a comparator of interest
Ciaffi et al., 2020[6]	Not a comparator of interest
Ciaffi et al., 2022[7]	Duplicate
Tillie-Leblond et al., 2008[8]	Not a comparator of interest
Grau et al., 1996[9]	Not a comparator of interest
Friedman et al., 1996[10]	Not a comparator of interest
Airo et al., 2007[11]	Not a comparator of interest
Davas et al., 1999[12]	Not a comparator of interest
Bruni et al., 2020[13]	Not a comparator of interest
Domiciano et al., 2011[14]	Not a comparator of interest
Iudici et al., 2015[15]	Not a comparator of interest
Tsuji et al., 2020[16]	No intervention of interest
Shi et al., 2009[17]	Wrong study design
Okamoto et al., 2016[18]	Wrong study design
Fu et al., 2019[19]	Wrong study design
Chen et al., 2022[20]	Wrong study design
Adler et al., 2018[21]	Wrong study design

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PICO 50: In rheumatic disease patients with ILD, what is the impact of calcineurin inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 50, we provide indirect evidence from PICO 30 (calcineurin inhibitors vs no calcineurin inhibitors as first line ILD treatment) and PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 30 and Low for PICO 25. An additional downgrade due to indirect comparison for PICO 50 resulted in a rating of Very low (for mycophenolate) and Very low (for calcineurin inhibitors).

Key Findings from PICO 30: indirect evidence from 5 observational studies:

- Two observational studies demonstrated the benefit of initiating a calcineurin inhibitor in combination with prednisolone as opposed to prednisolone alone as first-line therapy for IIM-ILD.
- Two observational studies present clinical outcomes data for complex treatment regimens with and without tacrolimus. Because of the multifaceted nature of these regimens, these studies do not directly address PICO 30.
- One observational study comparing the association of drug use on ILD progression showed insignificant differences between TAC, MTX, and LEF, however, the association between LEF use and the risk of ILD progression was significant in subgroups with poor lung function.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 2 observational studies):

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5

deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 30 and PICO 25.

Table 50-1. PICO 50: Excluded Studies

References	Reasons for exclusion
Hozumi et al. 2019[1]	Not a comparator of interest
Takada et al. 2020[2]	Not a comparator of interest
Tsuji et al. 2020[3]	Not a comparator of interest
Hanaoka et al. 2019[4]	No population of interest
Okamoto et al. 2016[5]	Not a comparator of interest

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4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 30

1. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases complicated with dermatomyositis: A retrospective analysis. *Medicine*. 2022;101(24):e29108. doi:https://dx.doi.org/10.1097/MD.0000000000029108
2. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
3. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
4. Kurita T, Yasuda S, Oba K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology (Oxford, England)*. 2015;54(1):39-44. doi:https://dx.doi.org/10.1093/rheumatology/keu166
5. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

PICO 51: In rheumatic disease patients with ILD, what is the impact of TNF inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 51, we provide indirect evidence from PICO 31 (anti-TNF therapy compared to no anti-TNF therapy as first line ILD treatment) and PICO 25 (mycophenolate compared to no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very Low for PICO 31. An additional downgrade due to indirect comparison for PICO 51 resulted in a rating of Very low (for mycophenolate) and Very low (for anti-TNF therapy).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 31: indirect evidence from 4 observational studies

- Four observational studies were included, one of which only provided data on infectious complications. None of these studies provide direct evidence that specifically addresses whether anti-TNF therapy is beneficial compared to no anti-TNF therapy as a first-line treatment for CTD-ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 31.

Table 51-1. PICO 51: Excluded Studies

References	Reasons for exclusion
Dixon et al. 2010 [1]	No intervention of interest
Chen et al. 2022 [2]	Wrong study design
Kang et al. 2020 [3]	Not a comparator of interest

References for PICO 51

1. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Annals of the rheumatic diseases*. 2010;69(6):1086-91.
2. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism.* 2020;50(3):401-408.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022
5.

References for Included Studies for PICO 31

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
2. Ma J, Sun J, Wang Y, Li G, Li M, Zhu Y. Efficacy of infliximab plus conventional therapy in dermatomyositis/polymyositis with interstitial lung disease: A prospective cohort study. *International Journal of Clinical and Experimental Medicine*. 2017;10(4):6819-6827.
3. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
4. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Annals of the rheumatic diseases*. 2010;69(6):1086-91. doi:https://dx.doi.org/10.1136/ard.2009.120626
5.

PICO 52: In rheumatic disease patients with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 52, we provide indirect evidence from PICO 34 (IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment) and PICO 25 (mycophenolate compared to no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for both PICO 25 and PICO 34. An additional downgrade due to indirect comparison for PICO 52 resulted in a rating of Very low.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 34: indirect evidence from 4 studies (2 RCTs, and 2 observational studies):

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest

tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.

- The aforementioned study's preceding phase 2 randomized controlled trial demonstrated slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a posthoc analysis of the aforementioned RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.
- One observational study of SSc patients reported no difference for FVC% predicted with tocilizumab vs without tocilizumab at 12 months.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 34.

Table 52-1. PICO 52: Excluded Studies

References	Reasons for exclusion
Suleman et al. 2021[1]	Wrong study design

References for PICO 52

1. Suleman Y, Clark KEN, Cole AR, Ong VH, Denton CP. Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase-positive patients. *Rheumatology (Oxford, England)*. 2021;60(8):3945-3946.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 34

1. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2020;8(10):963-974. doi:https://dx.doi.org/10.1016/S2213-2600(20)30318-0
2. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630-2640. DOI: 10.1016/s0140-6736(16)00232-4.
3. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(7):1301-1310. doi:https://dx.doi.org/10.1002/art.41668
4. Kuster S, Jordan S, Elhai M, et al. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD open. 2022;8(2)
5.

PICO 53: In rheumatic disease patients with ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 53, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment), PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment), and PICO 116 (adding anti-CD20 antibody compared to adding mycophenolate after 1st line therapy) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25, Very low for PICO 33, and Very low for PICO 116. An additional downgrade due to indirect comparison for PICO 53 resulted in a rating of Very low (for mycophenolate) and Very low (for anti-CD20 antibody and for anti-CD20 antibody after 1st line therapy).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 33: direct evidence from 5 studies (1 RCT, 4 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.

- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.

Key Findings from PICO 116: indirect evidence from 1 observational study

- Evidence from one retrospective cohort study suggests that there is no difference between adding rituximab and mycophenolate compared to mycophenolate alone on disease-related outcomes with the exception of a relative decrease in average prednisone dose in those given rituximab (RTX) with or without mycophenolate (MMF) vs. MMF alone. The rate of adverse events in the control group was not reported.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25, PICO 33, and PICO 116.

Table 53-1. PICO 53: Excluded Studies

References	Reasons for exclusion
Korsten et al. 2020[1]	No intervention of interest
Daoussis et al. 2012[2]	No intervention of interest
Yusof et al. 2017[3]	Not a comparator of interest
Kelly et al. 2021[4]	No intervention of interest
Langlois et al. 2020[5]	No intervention of interest

References for PICO 53

1. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595.
2. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. *Clinical and experimental rheumatology*. 2012;30(2 Suppl 71):S17-22.

3. Md Yusof MY, Kabia A, Darby M, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. *Rheumatology (Oxford, England)*. 2017;56(8):1348-1357.
4. Kelly CA, Nisar M, Arthanari S, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. *Rheumatology (Oxford, England)*. 2021;60(4):1882-1890.
5. Langlois V, Gillibert A, Uzunhan Y, et al. Rituximab and Cyclophosphamide in Antisynthetase Syndrome-related Interstitial Lung Disease: An Observational Retrospective Study. *The Journal of rheumatology*. 2020;47(11):1678-1686.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

5. Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Annals of the rheumatic diseases*. 2015;74(6):1188-94. doi:https://dx.doi.org/10.1136/annrheumdis-2013-204522
6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.

PICO 54: In rheumatic disease patients with ILD, what is the impact of abatacept compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 54, we provide indirect evidence from PICO 32 (abatacept vs no abatacept as first line ILD treatment) and PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 32 and Low for PICO 25. An additional downgrade due to indirect comparison for PICO 54 resulted in a rating of Very low (for mycophenolate) and Very low (for abatacept).

Key findings from PICO 32: indirect evidence from 3 observational studies:

- One retrospective study without a comparator group evaluated 16 RA-ILD patients who received abatacept for at least one year. No patients had a worsening in ILD severity during the study period.
- In one small retrospective study that included 44 patients who received abatacept and 31 patients who received a JAKi, there was no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.
- Although the differences were small, one retrospective study of RA-ILD patients demonstrated that receiving abatacept vs any form of TNFi may be associated with a decreased risk of ILD exacerbation or serious respiratory complications.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 32 and PICO 25.

Table 54-1. PICO 54: Excluded Studies

References	Reasons for exclusion
Nakashita et al. 2016[1]	Not a comparator of interest
Tardella et al. 2022[2]	No intervention of interest
Kang et al. 2020[3]	No intervention of interest

References for PICO 54

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9.
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712.
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 34

1. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2020;8(10):963-974. doi:https://dx.doi.org/10.1016/S2213-2600(20)30318-0
2. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630-2640. DOI: 10.1016/s0140-6736(16)00232-4.
3. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(7):1301-1310. doi:https://dx.doi.org/10.1002/art.41668
4. Kuster S, Jordan S, Elhai M, et al. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD open. 2022;8(2)

PICO 55. In rheumatic disease patients with ILD, what is the impact of JAK inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- **Certainty of evidence across all critical outcomes:** Very low

Key findings:

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5-associated ILD.[1]
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.[2]

Summary: 2 observational studies indirectly addressed this PICO.

One retrospective study (Fan et al. 2022[1] compared outcomes for MDA5-ILD patients who received tofacitinib (n=26) vs those who received tacrolimus (TAC)(n=35). The 6-month (38.5% vs 62.9%; P = 0.03) and 1-year (44.0% vs 65.7%; P = 0.03) mortality rates in the TOF group were significantly lower than those in the TAC group. Although more patients in the TAC group experienced RP-ILD (22 vs 13), the mortality rates for the TOF group were lower than the TAC group for patients with RP-ILD (76.9% vs 95.5%, P = 0.02 at six months; 84.6% vs 100.0%, p= 0.02 at one year).

In a study by Tardella et al. 2022,[2] 31 RA-ILD patients who received a JAKi and 44 patients who received abatacept were retrospectively studied using a computer-aided method (CaM) to assess changes in (HRCT) fibrosis percentage. Patients were classified as worsened (15% more fibrosis), stable, or improved (15% less fibrosis). After 18 months, 5 (11.4%) patients showed a HRCT deterioration, 32 (72.6%) were considered stable, and 7 (16.0%) patients showed an HRCT improvement in the ABA group. In the JAKis group 5 (16.1%) patients showed a HRCT deterioration, 20 (64.5%) were considered stable, and 6 (19.4%) patients showed an HRCT improvement. There was no significant change in mean FVC, DLCO, or CT fibrosis scores. Abatacept was not first-line treatment for this study and patients concomitantly taking methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs) and/or glucocorticoids at a dose of less than 10 mg daily prednisone or equivalent were included.

Table 55-1: impact of JAK inhibitors vs no JAK inhibitors as first line ILD treatment

Author, year	Study design	Risk of bias	Time of reassessment	Population Description	Screening or assessment measures	Results
Fan et al. 2022[1]	Retrospective observational study	High		MDA5-ILD patients treated with either Tofacitinib or TAC	26 patients were treated with TOF and 35 were treated with TAC	Entire group TOF TAC 6-month mortality 10 (38.5%) 22 (62.9%) P=0.03 1-year mortality 11 (44.0%) 23 (65.7%) p=0.03 RP-ILD TOF TAC 6-month mortality 10 (76.9%) 21 (95.5%) p=0.02 1-year mortality 11 (84.6%) 22 (100%) p=0.02

Tardella et al. 2022[2]	Retrospective observational study	High		75 RA-ILD patients who received either JAKis or abatacept. Seventy-five patients (69.3% women) were evaluated, 31 received a JAKi while 44 received ABA.	31 patients who received a JAKi and 44 patients who received Abatacept. Computer-aided method (CaM) used to assess changes in (HRCT) fibrosis percentage and classify patients as worsened (15% more), stable, or improved (15% less) fibrosis after 18 months.	Abatacept JAKis Time 0 Time 18 Time 0 Time 18 DLCO 58.69 61.36 59.72 62.77 FVC 82.29 81.24 81.18 79.59 HRCTcam 19.41 18.94 18.54 17.52 All p values NS CT deterioration Stability Improved ABA 5 (11.4%) 32 (72.6%) 7 (16%) JAKis 5 (16%) 20 (65.5%) 6 (19.4%)

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w

PICO 56: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 56, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 38 (nintedanib vs no nintedanib as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Low to Moderate for PICO 38. An additional downgrade due to indirect comparison for PICO 56 resulted in a rating of Low.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.

    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs (SENSCIS, INBUILD) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS, INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 38.

Table 56-1. PICO 56: Excluded Studies

Reference	Reason for exclusion
Kreuter et al. 2022[1]	Not a comparator of interest

References for PICO 56

1. Kreuter M, Del Galdo F, Miede C, et al. Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis. *Arthritis research & therapy*. 2022;24(1):19.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076
2. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681
4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020
5. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1

6. Assassi S, Distler O, Allanore Y, et al. Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial. *ACR Open Rheumatology*. 2022;doi:https://dx.doi.org/10.1002/acr2.11483
7. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. *Annals of the rheumatic diseases*. 2020;79(11):1478-1484. doi:https://dx.doi.org/10.1136/annrheumdis-2020-217331
8. Volkmann ER, Kreuter M, Hoffmann-Vold AM, et al. Dyspnoea and cough in patients with systemic sclerosis-associated interstitial lung disease in the SENSCIS trial. *Rheumatology (Oxford, England)*. 2022;doi:https://dx.doi.org/10.1093/rheumatology/keac091
9. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
10. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory investigation*. 2021;59(2):252-259. doi:https://dx.doi.org/10.1016/j.resinv.2020.10.005
11. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402
12. Maher TM, Mayes MD, Kreuter M, et al. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(4):671-676. doi:https://dx.doi.org/10.1002/art.41576

PICO 57: In rheumatic disease patients with ILD, what is the impact of pirfenidone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 57, we provide indirect evidence from PICO 39 (pirfenidone compared to no pirfenidone as first line ILD treatment) and PICO 25 (mycophenolate compared to no mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Low for PICO 39. An additional downgrade due to indirect comparison for PICO 57 resulted in a rating of Very low (for mycophenolate) and Very Low (for pirfenidone).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 39: direct evidence from 3 RCTs

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition,

hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.

- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated based on an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 39.

Table 57-1. PICO 57: Excluded Studies

References	Reasons for exclusion
Li et al. 2016[1]	No comparator of interest

References for PICO 57

1. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Scientific reports*. 2016;6:33226. doi:https://dx.doi.org/10.1038/srep33226

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 39

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270
3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3

PICO 58: In rheumatic disease patients with ILD, what is the impact of IVIG compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 58, we provide indirect evidence from PICO 25 (mycophenolate compared to no mycophenolate as first line ILD treatment) and PICO 40 (IVIG vs no IVIG as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very low for PICO 40 (no studies addressing). An additional downgrade due to indirect comparison for PICO 58 resulted in a rating of Very low (for mycophenolate) and Very low (for IVIG).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs and 1 observational study), indirect evidence from 1 observational study

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 25.

Table 58-1. PICO 58: Excluded Studies

References	Reasons for exclusion
Danieli et al. 2014[1]	No intervention of interest

References for PICO 58

1. Danieli MG, Gambini S, Pettinari L, Logullo F, Veronesi G, Gabrielli A. Impact of treatment on survival in polymyositis and dermatomyositis. A single-centre long-term follow-up study. *Autoimmunity reviews*. 2014;13(10):1048-54.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

PICO 59: In rheumatic disease patients with ILD, what is the impact of oral prednisone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 59, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 36 (daily oral prednisone vs no daily oral prednisone as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very low for PICO 36 (no evidence addressing). An additional downgrade due to indirect comparison for PICO 59 resulted in a rating of Very low (for mycophenolate) to Very low (for daily oral prednisone).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25.

Table 59-1. PICO 59: Excluded Studies

References	Reasons for exclusion
Perez-Campos et al. 2012[1]	Not a comparator of interest
Ando et al. 2013[2]	Not a comparator of interest
Hozumi et al. 2019[3]	Not a comparator of interest
Bodolay et al. 2005[4]	Not a comparator of interest

Friedman et al. 1996[5]	Wrong study design
Chen et al. 2022[6]	Not a comparator of interest
Zamora-Legoff et al. 2016[7]	Not a comparator of interest
Adler et al. 2018[8]	Not a comparator of interest

References for PICO 59

1. Perez Campos D, Estevez Del Toro M, Pena Casanovas A, Gonzalez Rojas PP, Morales Sanchez L, Gutierrez Rojas AR. Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis? *Reumatologia clinica*. 2012;8(2):58-62.
2. Ando K, Motojima S, Doi T, et al. Effect of glucocorticoid monotherapy on pulmonary function and survival in Japanese patients with scleroderma-related interstitial lung disease. *Respiratory investigation*. 2013;51(2):69-75.
3. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517.
4. Bodolay E, Szekanecz Z, Devenyi K, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology (Oxford, England)*. 2005;44(5):656-61.
5. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Seminars in arthritis and rheumatism*. 1996;26(1):459-67.
6. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
7. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9.
8. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

PICO 60: In rheumatic disease patients with ILD, what is the impact of intravenous methylprednisolone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very Low**

Due to the lack of direct evidence for PICO 60, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) below. No PICO addressed the effectiveness of intravenous methylprednisone as first line ILD treatment. The certainty of evidence across all critical outcomes was rated Low for PICO 25. An additional downgrade due to indirect comparison for PICO 60 resulted in a rating of Very low.

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 25.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.

2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

PICO 61: In rheumatic disease patients with ILD, what is the impact of plasma exchange compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 61, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 41 (plasma exchange vs no plasma exchange as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very low for PICO 41. An additional downgrade due to indirect comparison for PICO 61 resulted in a rating of Very low (for mycophenolate) to Very low (for plasma exchange).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 41: indirect evidence from 1 observational study

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 41.

Table 61-1. PICO 61: Excluded Studies

References	Reasons for exclusion
Tsuji et al. 2020[1]	No comparator of interest

References for PICO 61

1. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 41

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7.

PICO 62: In rheumatic disease patients with ILD, what is the impact of methotrexate compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 62, we provide indirect evidence from PICO 28 (methotrexate vs no methotrexate as first line ILD treatment) and PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 28 and PICO 33.

Key Findings from PICO 28: indirect evidence from 3 observational studies

- 3 observational studies of 381 RA-ILD patients reported that 60 (30.6%) patients classified as "progressive," and 71 (38.3%) patients classified as "stable" were taking methotrexate.
- 1 observational study reported that treatment with MTX, LEF, and tacrolimus were not associated with progression of RA-ILD.
- 1 observational study reported that treatment with MTX was not associated with better survival (HR 0.58, 95% CI: 0.33 to 1.01).

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 28 and PICO 33.

Table 62-1. PICO 62: Excluded Studies

References	Reasons for exclusion
Tille-Leblond et al. 2008[1]	Wrong study design
Fu et al. 2019 [2]	No comparator of interest
Chen et al. 2022 [3]	No comparator of interest
Zamora-Legoff et al. 2016 [4]	No comparator of interest

References for PICO 62

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.
2. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116.
3. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9.

References for Included Studies for PICO 28

1. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
2. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
3. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093

2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
5. Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Annals of the rheumatic diseases*. 2015;74(6):1188-94. doi:https://dx.doi.org/10.1136/annrheumdis-2013-204522
6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003

PICO 63: In rheumatic disease patients with ILD, what is the impact of leflunomide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 63, we provide indirect evidence from PICO 27 (leflunomide vs no leflunomide as first line ILD treatment) and PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 27 and PICO 33.

Key Findings from PICO 27: direct evidence from 2 observational studies:

- One single-center retrospective cohort study assessed the risk of infection of patients receiving methotrexate/leflunomide (n=54) vs. no therapy (n=48). The infection rate in the MTX/LEF group vs. no therapy group was 7.4 vs. 6.6 per 100 person-year (py), respectively.
- A multicenter prospective observational cohort study of RA-ILD patients exposed to either LEF, MTX, or TAC demonstrated that LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, p=0.031 and an increased risk of ILD progression in patients with decreased lung function (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression and were at higher risk for ILD progression.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later time points), and use of a surrogate outcome (PFT data) limit the utility of these data.

- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 27 and PICO 33.

Table 63-1. PICO 63: Excluded Studies

References	Reasons for exclusion
Chen et al. 2022[1]	No comparator of interest
Zamora-Legoff et al. 2016[2]	No comparator of interest

References for PICO 63

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004.
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. ‘

References for Included Studies for PICO 27

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
2. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461

3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
5. Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Annals of the rheumatic diseases*. 2015;74(6):1188-94. doi:https://dx.doi.org/10.1136/annrheumdis-2013-204522
6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.

PICO 64: In rheumatic disease patients with ILD, what is the impact of azathioprine compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 64, we provide indirect evidence from PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) and PICO 33 (anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 29 and PICO 33.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on “standard therapy” who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.

- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 29 and PICO 33.

Table 64-1. PICO 64: Excluded Studies

References	Reasons for exclusion
Tille-Leblond et al. 2008[1]	No comparator of interest
Grau et al. 1996[2]	No comparator of interest
Friedman et al. 1996[3]	Wrong study design
Okamoto et al. 2016[4]	No comparator of interest
Kelly et al. 2021[5]	No intervention of interest
Amlani et al. 2020[6]	No intervention of interest
Adler et al. 2018[7]	No comparator of interest
Matson et al. 2022[8]	No comparator of interest

References for PICO 64

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.
2. Grau JM, Miro O, Pedrol E, et al. Interstitial lung disease related to dermatomyositis. Comparative study with patients without lung involvement. *Journal of Rheumatology*. 1996;23(11):1921-1926.
3. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Seminars in arthritis and rheumatism*. 1996;26(1):459-67.

4. Okamoto M, Fujimoto K, Sadohara J, et al. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. *Respiratory Investigation*. 2016;54(6):445-453.
5. Kelly CA, Nisar M, Arthanari S, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. *Rheumatology (Oxford, England)*. 2021;60(4):1882-1890.
6. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147.
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8. Matson SM, Baqir M, Moua T, et al. Treatment Outcomes for Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Real-World, Multisite Study of the Impact of Immunosuppression on Pulmonary Function Trajectory. *Chest*. 2022 Dec 5:S0012-3692(22)04205-2. doi: 10.1016/j.chest.2022.11.035. Epub ahead of print.

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org \

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461

3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
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5. Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Annals of the rheumatic diseases*. 2015;74(6):1188-94. doi:https://dx.doi.org/10.1136/annrheumdis-2013-204522
6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.

PICO 65: In rheumatic disease patients with ILD, what is the impact of cyclophosphamide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes**: Very low**

<u>Key Findings</u>:

1. Evidence from one RCT[1] suggested no difference in mortality risk among patients randomized to cyclophosphamide or rituximab at 6 months of follow-up; however, only one death occurred in each study arm (very low quality of evidence).
    a. *Patients with RP-ILD (indirect evidence):* Evidence from the Maher et al. (RECITAL) 2023[2] trial suggested no difference in mortality risk among patients with rapidly progressive ILD (indirect evidence for first-line therapy); however, the event rate was very small (48 weeks of follow-up).
2. Adverse events (AEs)
    a. Evidence from one RCT[1] suggested a 5.4-fold higher risk of any AEs (composite outcome) among individuals randomized to cyclophosphamide than those randomized to rituximab at 6 months of follow-up.
        i. *Patients with RP-ILD (indirect evidence):* Evidence from the Maher, et al. (RECITAL) 2023[2] trial indicated fewer adverse events among participants receiving rituximab (445 events) than those receiving cyclophosphamide (646 events) (48 weeks of follow-up).
    b. Evidence from one RCT[1] suggested no difference between the risk of single AEs among individuals randomized to cyclophosphamide than among those randomized to rituximab at 6 months of follow-up; however, the event rate was very small (very low quality of evidence).
        i. *Patients with RP-ILD (indirect evidence):* Evidence from the Maher, et al. (RECITAL) 2023[2] trial indicated a higher rate of gastrointestinal disorders (170 vs. 71 events), general disorders, and administration site reactions (91 vs. 52 events) and nervous system disorders among patients in the cyclophosphamide group vs. rituximab (48 weeks of follow-up).
    c. Evidence from one RCT[1] suggested no difference in the study discontinuation rate among individuals randomized to cyclophosphamide and rituximab at 6 months of follow-up; however, the event rate was very small (very low quality of evidence).
        i. *Patients with RP-ILD (indirect evidence):* Evidence from the Maher et al. (RECITAL) 2023[2] trial reported a similar study discontinuation rate in both groups—RR 0.54; 95% CI: 0.27 to 1.10 (48 weeks of follow-up).

Summary:

We included two studies that directly apply to this question—one RCT (Sircar et al., 2018[1]) and one retrospective data analysis (Yilmaz et al., 2021[3]). In the RCT (Sircar et al., 2018[1]), adults (n=60) with systemic sclerosis–related interstitial lung diseases were randomized either to rituximab (RTX; 1000 mg; n=30) or to cyclophosphamide (CYC; 500 mg/m^2; n=30). This trial contributed data for adverse events, study discontinuation, and % change in forced vital capacity (FVC). Outcomes were ascertained at 6 months of follow-up. The retrospective analysis (Yilmaz et al., 2021[2]) included 61 adults with systemic sclerosis with pulmonary involvement who received either rituximab (n=27) or cyclophosphamide (n=34) for a minimum of 24 months between 1996 and 2018 in Turkey.[3] This study contributed data for adverse events (i.e., leucopenia), % change in FVC, and carbon monoxide diffusion capacity of the lung (DLco). The RCT was rated a high risk of bias. The quality concerns were due to the lack of blinding of patients, not accounting for missing data, and being statistically underpowered to detect a difference in adverse events. The study by Yilmaz et al., 2021[3] was rated as having a serious risk of bias (ROBINS-I quality assessment tool) due to patients in both groups not being matched and being different at baseline for a number of characteristics, including time from the first respiratory symptoms (mean of 133 months [SD 120] months in the RTX group and 65 months [SD 52] in the CYC group). The allocation to a group was based on the clinical indication.

We also present data from the Rituximab Versus Intravenous Cyclophosphamide In Patients with Connective Tissue Disease-Associated Interstitial Lung Disease in the UK (RECITAL; Maher, et al.[2]) with 101 patients with severe or rapidly progressive ILD. Patients were randomized (1:1) to receive rituximab (n=51; 1000 mg at weeks 0 and 2 intravenously) or cyclophosphamide (n=50; 600 mg/m² body surface area every 4 weeks intravenously for six doses). This trial demonstrated no difference between the groups in terms of mortality risk, study discontinuation rate, carbon monoxide diffusion capacity of the lung, forced vital capacity, and quality of life. This trial

Harms

The RCT suggested a 5-fold higher risk of any AEs (composite outcome) among individuals randomized to CYC (21/30 [70.0%]) than those with RTX (9/30 [30.0%])— OR 5.44; 95% CI: 1.80 to 16.43).[1] The absolute difference ranged from 135 more to 576 more patients experiencing AEs per every 1,000 taking CYC vs. RTX at 6 months of follow-up (low quality of evidence). The rate for any single adverse events (AEs) and discontinuation did not differ statistically between the groups at 6 months of follow-up in the RCT and observational study (very low quality of evidence). However, the number of events was very small.

The RECITAL[2] trial indicated a higher risk of any adverse events in the cyclophosphamide group compared to rituximab (646 events in 48 patients and 445 events in 49 patients, respectively).

Mortality

One patient died in each arm at 6 months of follow-up in the Sircar et al., 2018 trial.[1] These data are insufficient to conclude a differential mortality risk between CYC and RTX (very low quality of evidence).

Patients with RP-ILD (indirect evidence): Evidence from the Maher, et al. (RECITAL) 2023[2] suggested no difference in mortality risk among patients with rapidly progressive ILD (indirect evidence for first-line therapy); however, the event rate was also very small (48 weeks of follow-up).

Forced vital capacity, % change

The RCT assessed a change in % FVC at 6 months of follow-up. This study suggested a greater increase of FVC in the RTX group than in the CYC group—the mean difference was 9.46 (95% CI: 3.01 to 15.90). The % FVC did not change for patients in the CYC group from baseline to follow-up (from 59.3 [SD 12.96] to 58.1 [SD 11.23]; p=0.5), while individuals randomized to RTX improved from 61.3 (SD 11.28) to 67. 52 (SD 13.59) p=0.002. The observational study suggested the FVC benefit of CYC, compared to RTX at 3 months (MD 4.30 [95% CI: 0.76, 7.84]) and 12 months (MD 8.50 [95% CI: 4.59, 12.41] of follow-up. However, there was no statistically significant difference at 6- and 24 months of follow-up (MD 2.20 [95% CI: -1.52, 5.92]; MD -0.10 [95% CI: -4.26, 4.06], respectively; very low quality of evidence).

Patients with RP-ILD (indirect evidence): Evidence from the Maher, et al. (RECITAL) 2023[2] suggested no difference in FVC (mL) between the CYC and RXT groups at 24- and 48 weeks of follow-up.

Carbon monoxide diffusion capacity of the lung, % change

The study by Yılmaz et al., 2021[3] compared the effects of CYC and RTX on % DLco change at 3, 6, 12, and 24 months of follow-up. The study suggested no difference between the groups at 3 to 12 months of follow-up. However, patients in the RTX group demonstrated a greater increase of % DLco than those taking CYC at 24 months (very low quality of evidence).

Patients with RP-ILD (indirect evidence): Evidence from Maher, et al. (RECITAL) 2023[2] suggested no difference in DLCO (mL/min per kPa) between the CYC and RXT groups at 24- and 48 weeks of follow-up.

Quality of Life

Patients with RP-ILD (indirect evidence): Evidence from Maher, et al. (RECITAL) 2023[2] suggested no difference in any of the three used quality of life estimates between the CYC and RXT groups at 24- and 48 weeks of follow-up. No direct evidence was identified.

Table 65-1. Evidence Summary—Cyclophosphamide compared to rituximab for early diffuse scleroderma lung disease

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide	rituximab	Relative (95% CI)	Absolute (95% CI)		
Mortality from RCT												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	1/30 (3.3%)	1/30 (3.3%)	**OR 1.00** (0.06 to 16.76)	**0 more per 1,000** (from 31 fewer to 333 more)	⨁◯◯◯ Very low	CRITICAL
Study Discontinuation (follow-up: 6 months)												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	1/32 (3.1%)	2/32 (6.3%)	**OR 0.48** (0.04 to 5.62)	**31 fewer per 1,000** (from 60 fewer to 210 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Upper respiratory tract infection												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	2/30 (6.7%)	2/30 (6.7%)	**OR 1.00** (0.13 to 7.60)	**0 fewer per 1,000** (from 57 fewer to 285 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Pneumonia (RCT)												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	4/30 (13.3%)	1/30 (3.3%)	**OR 4.46** (0.47 to 42.51)	**100 more per 1,000** (from 17 fewer to 561 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Pneumonia (Observational data)												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	1/34 (2.9%)	1/27 (3.7%)	**OR 0.79** (0.05 to 13.21)	**8 fewer per 1,000** (from 35 fewer to 300 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Herpes zoster												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	3/30 (10.0%)	1/30 (3.3%)	**OR 3.22** (0.32 to 32.89)	**67 more per 1,000** (from 22 fewer to 498 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Cholecystitis (requiring cholecystectomy)												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide	rituximab	Relative (95% CI)	Absolute (95% CI)		
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	0/30 (0.0%)	1/30 (3.3%)	**OR 0.32** (0.01 to 8.24)	**22 fewer per 1,000** (from 33 fewer to 188 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Premature ovarian failure												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	2/32 (6.3%)	0/32 (0.0%)	**OR 5.33** (0.25 to 115.50)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Gangrene												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	1/30 (3.3%)	0/30 (0.0%)	**OR 3.10** (0.12 to 79.23)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Malignancy												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	1/30 (3.3%)	0/30 (0.0%)	**OR 3.10** (0.12 to 79.23)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Leukopenia (RCT)												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	2/30 (6.7%)	0/30 (0.0%)	**OR 5.35** (0.25 to 116.31)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Yılmaz et al., 2021[3]	observational	very serious	not serious	not serious	very serious	none	0/34 (0.0%)	1/27 (3.7%)	**OR 0.26** (0.01 to 6.54)	**27 fewer per 1,000** (from 37 fewer to 164 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Transfusion reactions												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	3/30 (10.0%)	0/30 (0.0%)	**OR 7.76** (0.38 to 157.14)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Urinary tract infections												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	2/30 (6.7%)	1/30 (3.3%)	**OR 2.07** (0.18 to 24.15)	**33 more per 1,000** (from 27 fewer to 421 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Vomiting												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	very serious[c]	none	4/30 (13.3%)	0/30 (0.0%)	**OR 10.36** (0.53 to 201.45)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Events at 6 months - Composite AE Outcome from RCT												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	not serious	serious[c]	none	21/30 (70.0%)	9/30 (30.0%)	**OR 5.44** (1.80 to 16.43)	**400 more per 1,000** (from 135 more to 576 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide	rituximab	Relative (95% CI)	Absolute (95% CI)		
Forced vital capacity, % change - At 3 months of follow-up												
Yılmaz et al., 2021[2]	observational	very serious	not serious	serious[d]	serious	none	34	27	-	MD **4.3 higher** (0.76 higher to 7.84 higher)	⨁◯◯◯ Very low	IMPORTANT
Forced vital capacity, % change - At 6 months of follow-up (RCT)												
Sircar et al., 2018[1]	randomised trials	serious[a,b]	not serious	serious[d]	very serious[c]	none	30	30	-	MD **9.46 higher** (3.01 higher to 15.9 higher)	⨁◯◯◯ Very low	IMPORTANT
Yılmaz et al., 2021[2]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **2.2 higher** (1.52 lower to 5.92 higher)	⨁◯◯◯ Very low	IMPORTANT
Forced vital capacity, % change - At 12 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **8.5 higher** (4.59 higher to 12.41 higher)	⨁◯◯◯ Very low	IMPORTANT
Forced vital capacity, % change - At 24 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **0.1 lower** (4.26 lower to 4.06 higher)	⨁◯◯◯ Very low	IMPORTANT
Carbon monoxide diffusion capacity of the lung, % change - At 3 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **3.7 lower** (8.48 lower to 1.08 higher)	⨁◯◯◯ Very low	IMPORTANT
Carbon monoxide diffusion capacity of the lung, % change - At 6 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **5.5 lower** (11.62 lower to 0.62 higher)	⨁◯◯◯ Very low	IMPORTANT
Carbon monoxide diffusion capacity of the lung, % change - At 12 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **0.4 lower** (4.63 lower to 3.83 higher)	⨁◯◯◯ Very low	IMPORTANT
Carbon monoxide diffusion capacity of the lung, % change - At 24 months of follow-up												
Yılmaz et al., 2021[3]	observational	very serious	not serious	serious[d]	very serious	none	34	27	-	MD **8.3 lower** (14.49 lower to 2.11 lower)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Unknown blinding
b. Unaccounted for missing data
c. Small study, underpowered to detect the difference (very small event rate)

Table 65-2: PICO 65: Cyclophosphamide (CYC) compared to rituximab (RTX) in Rapidly Progressive ILD

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Maher, T. et al. (RECITAL) 2023[2]	2b Phase; RCT (all outcomes from this trial presented here)	Moderate (recruitment was terminated preliminary that led to study not reaching statistical power to detect the difference)	24 and 48 weeks	Adults aged 18–80 years with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD, recruited across 11 specialist ILD or rheumatology centers in the UK	Patients were randomized (1:1) to receive rituximab (n=51; 1000 mg at weeks 0 and 2 intravenously) or cyclophosphamide (n=50; 600 mg/m² body surface area every 4 weeks intravenously for six doses).	**Mortality (48 weeks)** CYC: 4% (2/48) RTX: 6% (4/49) ***No difference*** **Adverse events (48 weeks)** CYC: 646 events in 48 pts RTX: 445 events in 49 pts ***Not Tested (more AEs reported in the CYC group compared to RTX)*** • Gastrointestinal disorders (170 vs 71 events), general disorders and administration site reactions (91 vs 52 events) and nervous system disorders (72 *vs* 35 events) were more common in the cyclophosphamide group than in the rituximab group. The rate of other AE was similar across both groups. **Study Discontinuation (48 weeks)** CYC: 9/50 RTX: 17/51 RR 0.54; 95% CI: 0.27 to 1.10, **no difference** **Carbon monoxide diffusion capacity of the lung, mL/min per kPa change** **24 weeks:** Adjusted difference: 0·186 (–0·054 to 0·425); p=0·425; ***no difference*** **48 weeks:** Adjusted difference: 0·117 (–0·137 to 0·372); p=0·372; ***no difference***

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						Forced vital capacity, mL change **24 weeks:** Adjusted difference: –40 (–153 to 74); p=0·493; ***no difference*** **48 weeks:** Adjusted difference: –58 (–178 to 62); p=0·345; ***no difference*** **Quality of Life** ED-5D **24 weeks:** Adjusted difference: 3·06 (–3·05 to 9·18) p=0·326; ***no difference*** **48 weeks:** Adjusted difference: 4·77 (–1·73 to 11·27) p=0·150; ***no difference*** KBILD Score **24 weeks:** Adjusted difference: 0·40 (–5·73 to 6·52) p=0·899; ***no difference*** **48 weeks:** Adjusted difference: 1·15 (–5·34 to 7·64) p=0·728; ***no difference*** SGRQ Score **24 weeks:** Adjusted difference: 0·63 (–5·64 to 6·91) p=0·843; ***no difference*** **48 weeks:** Adjusted difference: 2·82 (–3·69 to 9·34) p=0·396; ***no difference***

EQ-5D=European Quality of Life Five-Dimension. KBILD=King's Brief Interstitial Lung Disease. SGRQ=St George's Respiratory Questionnaire.

Table 65-3. PICO 65: Excluded Studies

Reference	Reason for Exclusion
Ciaffi et al. 2022[4]	Not a comparator of interest
Benad et al., 2022[5]	Not a comparator of interest
Chen et al. 2022[6]	Not a comparator of interest
Kelly et al. 2021[7]	Not a comparator of interest
Ciaffi et al. 2020[8]	Not a comparator of interest
Bruni et al. 2020[9]	Not a comparator of interest

Reference	Reason for Exclusion
Tsuji et al. 2020[10]	Not a comparator of interest
Kim et al. 2020[11]	Not a comparator of interest
Li et al. 2019[12]	Not a comparator of interest
Fu et al. 2019[13]	Not a comparator of interest
Adler et al. 2018[14]	Not a comparator of interest
Kundu et al. 2016[15]	Not a comparator of interest
Okamoto et al. 2016[16]	Not a comparator of interest
Perez-Campos et al. 2012[17]	Not a comparator of interest
Domiciano et al. 2011[18]	Not a comparator of interest
Shi et al. 2009[19]	Not a comparator of interest
Tillie-Leblond et al. 2008[20]	Not a comparator of interest
Airo et al. 2007[21]	Not a comparator of interest
Bodolay et al. 2005[22]	Not a comparator of interest
Davas et al. 1999[23]	Not a comparator of interest
Grau et al. 1996[24]	Not a comparator of interest
Friedman et al. 1996[25]	Not a comparator of interest

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PICO 66: In rheumatic disease patients with ILD, what is the impact of calcineurin inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 66, we provide indirect evidence from PICO 30 (calcineurin inhibitors vs no calcineurin inhibitors as first line ILD treatment) and PICO 33 (anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 30 and PICO 33.

Key Findings from PICO 30: indirect evidence from 4 observational studies:

- Two observational studies demonstrated the benefit of initiating a calcineurin inhibitor in combination with prednisolone as opposed to prednisolone alone as first-line therapy for IIM-ILD.
- Other observational studies present clinical outcomes data for complex treatment regimens with and without tacrolimus. Because of the multifaceted nature of these regimens, these two studies do not directly address PICO 30.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.

- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 30 and PICO 33.

Table 66-1. PICO 66 Excluded Studies

Reference	Reason for Exclusion
Hozumi et al., 2019[1]	No comparator of interest
Takada et al., 2020[2]	No comparator of interest
Tsuji et al., 2020[3]	No comparator of interest
Okamoto et al., 2016[4]	No comparator of interest

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References for Included Studies for PICO 30

1. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases

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2. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
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References for Included Studies for PICO 33

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6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.
7.

PICO 67: In rheumatic disease patients with ILD, what is the impact of TNF inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- One small observational cohort study of patients with RA-ILD suggested all-cause mortality rates per 1000 person-years (pyrs) were 53.0 (95% CI: 22.9 to 104.6) for rituximab (N=43) and 94.8 (95% CI: 74.7 to 118.7) for TNFi (N=309). This study suggested similar rates for RA-ILD as the underlying cause of death (14% [one patient] rituximab-treated vs. 16% [12 patients] TNFi-treated);[1] however, the study was not powered to detect the difference.
- One single-center retrospective cohort study assessed the risk of infection of patients receiving TNFi (alone or in combination with any other antirheumatic drug) (n=59) vs. non-TNFI biologic (rituximab and abatacept) (n=38). The infection rate in the TNFi group vs. non-TNFI biologic group was 1.8 vs. 13.5 per 100 person-year (py), respectively.[2]

Summary:

One retrospective cohort study reported mortality in patients with RA-ILD who received rituximab (n=43) or TNFi (infliximab, etanercept, adalimumab, and certolizumab pegol) (n=309) as their first biologic (see Table 67-1). Individuals were recruited to the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) between 2001 and 2011. The primary outcome was death, while secondary outcomes included (1) the proportion of deaths that listed RA-ILD as the underlying cause of death and (2) the proportion of deaths that listed RA-ILD anywhere on the death certificate.[1]

Deaths within the first 5 years following treatment were 8 in the RTX group (150.7 pyrs) and 76 in the TNFi group (801.3 pyrs). The all-cause mortality rates per 1000 pyrs were 53.0 (95% CI: 22.9 to 104.6) and 94.8 (95% CI: 74.7 to 118.7) for the rituximab and TNFi groups, respectively. The 5-year risk of mortality in rituximab-treated was approximately half that of the TNFi-treated (not significant; HR RTX vs. TNFI: unadjusted 0.53, 95% CI: 0.26 to 1.10, adjusted 0.49, 95% CI: 0.23 to 1.06). RA-ILD was listed on the death certificates of 71.4% of rituximab-treated vs. 36.5% of TNFi-treated, although similar rates were reported for RA-ILD as the underlying cause of death (14% rituximab-treated vs. 16% TNFi-treated).

We also included one retrospective cohort study that indirectly addressed this PICO question. Zamora-Legoff et al., 2016[2] assessed the rate of infection in RA-ILD patients who received various forms of immunosuppression. Of the 181 patients in the study, 59 received TNFi (alone or in combination with any other antirheumatic drug), and 38 received non-TNFI biologic (rituximab and abatacept), providing the basis for our assessment. Since patients receiving rituximab and abatacept were combined in this study, direct conclusions regarding the impact on rituximab specifically are difficult to draw, so the evidence is of very low quality. The infection rate per 100 pyrs in the TNFi group was 1.8 vs. 13.5 for the non-TNFi biologic group.

Table 67-1: PICO 67: TNF inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Druce et al., 2017[1]	Retrospective cohort study	High	5 years	RA-ILD patients recruited to the British Society for Rheumatology Biologics Register for RA (BSRBR-RA)	TNFi (infliximab, etanercept, adalimumab, and certolizumab pegol) (n=309) vs rituximab (n=43)	During 801.3 pyrs, 76 deaths occurred in the TNFi cohort and 8 deaths occurred within 150.7 pyrs in the RTX cohort. **All-cause mortality rates per 1000 pyrs:** RTX: 53.0 (95% CI: 22.9 to 104.6). TNFi: 94.8 (95% CI: 74.7 to 118.7) **RA-ILD listed as the underlying cause of death:** RTX: 1 (14%) death TNFi: 12 (16%) deaths **RA-ILD reported on death certificate:** RTX: 5 (71.4%) TNFi: 27 (36.5%)
Zamora-Legoff et al., 2016[2]	Retrospective cohort study	High	Risk of infection analyzed by person-year methods using time-dependent covariates started when med first	RA-ILD patients seen at Mayo Clinic Exclusion criteria: patients with concomitant rheumatological	59 patients on TNFi (alone or in combo with any other antirheumatic drug) 38 patients on non-TNFi biologic	Infection rates: 1.8 per 100 PY in TNFi group vs. 13.5 per 100 PY in non-TNFi biologic (rituximab and abatacept).

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
			used up until 30 days after stopping	disease (except for secondary SS)	(rituximab and abatacept)	

Table 67-2: PICO 67 Excluded Studies

Reference	Reason for Exclusion
Dixon et al., 2010[3]	No comparator of interest
Chen et al., 2022[4]	Wrong study design
Kang et al., 2020[5]	No intervention of interest

References

1. Druce KL, Iqbal K, Watson KD, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. *RMD open*. 2017;3(1):e000473. doi:https://dx.doi.org/10.1136/rmdopen-2017-000473
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
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5. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408. doi:https://dx.doi.org/10.1016/j.semarthrit.2019.11.010

PICO 68: In rheumatic disease patients with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 68, we provide indirect evidence from PICO 34 (IL-6 receptor antagonists (tocilizumab, sarilumab) vs no IL-6 receptor antagonists as first line ILD treatment) and PICO 33 (anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for PICO 33 and Low for PICO 34. An additional downgrade due to indirect comparison for PICO 68 resulted in a rating of Very low (for IL-6 receptor antagonists) and Very low (for anti-CD20 antibody).

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later time points), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 34: indirect evidence from 4 studies (2 RCTs, and 2 observational studies):

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring

metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.

- The aforementioned study's preceding phase 2 randomized controlled trial demonstrated a slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a post hoc analysis of the aforementioned RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.
- One observational study of SSc patients reported no difference for FVC% predicted with tocilizumab vs without tocilizumab at 12 months.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 33 and PICO 34.

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
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4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
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References for Included Studies for PICO 34

1. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2020;8(10):963-974. doi:https://dx.doi.org/10.1016/S2213-2600(20)30318-0
2. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630-2640. DOI: 10.1016/s0140-6736(16)00232-4.
3. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(7):1301-1310. doi:https://dx.doi.org/10.1002/art.41668
4. Kuster S, Jordan S, Elhai M, et al. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD open. 2022;8(2)
5.

PICO 69: In rheumatic disease patients with ILD, what is the impact of abatacept compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 69, we provide indirect evidence from PICO 32 (abatacept vs no abatacept as first line ILD treatment) and PICO 33 (anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for both PICO 32 and PICO 33.

Key findings from PICO 32: indirect evidence from 3 observational studies

- One retrospective study without a comparator group evaluated 16 RA-ILD patients who received abatacept for at least one year. No patients had a worsening in ILD severity during the study period.
- In one small retrospective study that included 44 patients who received abatacept and 31 patients who received a JAKi, there was no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.
- Although the differences were small, one retrospective study of RA-ILD patients demonstrated that receiving abatacept vs any form of TNFi may be associated with a decreased risk of ILD exacerbation or serious respiratory complications.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.

- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 32 and PICO 33.

Table 69-1. PICO 69: Excluded Studies

References	Reasons for exclusion
Nakashita et al., 2016 [1]	No comparator of interest
Tardella et al., 2022 [2]	No intervention of interest
Kang et al., 2020 [3]	No intervention of interest

References for PICO 69

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9.
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712.
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408.

References for Included Studies for PICO 32

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9. doi:https://dx.doi.org/10.1016/j.resinv.2016.03.001
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408. doi:https://dx.doi.org/10.1016/j.semarthrit.2019.11.010

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
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7.

PICO 70: In rheumatic disease patients with ILD, what is the impact of JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one observational study[1] suggested no difference in the respiratory events rate (i.e., composite outcome of hospitalizations and death rate) between patients with a history of JAK inhibitors and rituximab (HR 1.38, [95% CI: 0.36 to 5.28]); however, the sample size and the event rate were very small.
- One observational study[1] found no association between the type of pharmacotherapy and drug discontinuation rate (unadjusted HR 1.90, [95% CI: 0.63 to 5.73]); however, the sample size and the event rate were very small.

Summary:

This poor-quality retrospective observational study[1] was designed to compare the pulmonary safety of rituximab and JAK inhibitors in a cohort of patients with rheumatoid arthritis-associated ILD. The primary outcome was time to first respiratory event, which was defined as admission to the hospital with respiratory illness or death from respiratory cause while taking medications. There were 28 patients included in the JAK inhibitors group and 19 in the rituximab group, with mean intervention time of 1.1 (SD 0.62) and 2.14 (SD 1.0) years, respectively. The weighted mean age was 69.4 years (range 59 to 75 years). The mean duration of follow-up was 1.1 years and 2.1 years for JAK inhibitors and rituximab, respectively. The JAK inhibitor group has been previously treated with a greater number of biologics compared to the rituximab group. There was no statistically significant difference in respiratory survival in the JAK inhibitor group compared with the rituximab group (hazard ratio [HR] 1.38, [95% CI: 0.36 to 5.28]; p=0.64). The observed effect might not be attributed to the studied interventions.

Table 70-1. Retrospective Studies that do not provide data that allow quantitatively summarized

Author, year	Study type	Risk of Bias	Population Description	Outcomes	Results	GRADE Certainty Rating
Cronin et al., 2021[1]	Retrospective observational study	High	**Age (median, IQR):** JAK: 69 (62.3–75) Ritux: 70 (59–76) **% Female:** JAK:64.3% Rituximab: 73.7% RA with ILD or bronchiectasis ● RA with ILD on JAK (19) ● RA with bronchiectasis on JAK 7 ● RA with both on JAK 2 ● RA with ILD on Ritux 13 ● RA with bronchiectasis on Ritux 5 ● RA with both on Ritux 1	Respiratory event (RE): ● admission to the hospital with a respiratory illness (e.g., infection, ● ILD exacerbation ● Mortality	**Respiratory Events** ***JAK group (n=28)*** Respiratory events: 5 (18%) ● 7 (25.0%) hospitalizations ● 2 (7.14%) deaths ***Rituximab group (n=19)*** Respiratory events: 4 (21%) ● 4 (21.1%) hospitalizations ● 1 (5.3%) death Respiratory event survival: HR 1.38, (95%CI 0.36 to 5.28); p=0.64 **Drug Discontinuation** JAK group: 28.5% (8/28) Rituximab group: 36.8% (7/19) Unadjusted HR: 1.9 (95% CI 0.63 to 5.73); p = 0.251.	Very low

IQR: interquartile range; **RA**: rheumatoid arthritis; **HR**: Hazard ratio; **JAK**: Janus Kinase

Table 70-2. PICO 70: Excluded Studies

References	Reasons for exclusion
Tardella et al., 2022[2]	No comparator of interest
Fan et al., 2022[3]	No comparator of interest

References

1. Cronin O, McKnight O, Keir L, Ralston SH, Hirani N, Harris H. A retrospective comparison of respiratory events with JAK inhibitors or rituximab for rheumatoid arthritis in patients with pulmonary disease. *Rheumatology international*. 2021;41(5):921-928. doi:https://dx.doi.org/10.1007/s00296-021-04835-1

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3. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 71: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low to Very low**

Due to the lack of direct evidence for PICO 71, we provide indirect evidence from PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) and PICO 38 (nintedanib vs no nintedanib as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 33 and Moderate to Low for PICO 38. An additional downgrade due to indirect comparison for PICO 71 resulted in a rating of Low (for nintedanib) to Very low (for anti-CD20 antibody).

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.
    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs ((SENSCIS)(INBUILD)) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS)(INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 33 and PICO 38.

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
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3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
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6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076
2. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681
4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020

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9. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
10. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory investigation*. 2021;59(2):252-259. doi:https://dx.doi.org/10.1016/j.resinv.2020.10.005
11. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402
12. Maher TM, Mayes MD, Kreuter M, et al. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(4):671-676. doi:https://dx.doi.org/10.1002/art.41576

PICO 72: In rheumatic disease patients with ILD, what is the impact of pirfenidone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 72, we provide indirect evidence from PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) and PICO 39 (pirfenidone vs no pirfenidone as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 33 and Low for PICO 39. An additional downgrade due to indirect comparison for PICO 61 resulted in a rating of Very low.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later time points), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 39: direct evidence from 3 RCTs

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition, hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.

- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 33 and PICO 39.

Table 72-1. PICO 72: Excluded Studies

References	Reasons for exclusion
Li et al., 2016[1]	No comparator of interest

References for PICO 72

1. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Scientific reports*. 2016;6:33226.

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
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References for Included Studies for PICO 39

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270
3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3
4.

PICO 73: In rheumatic disease patients with ILD, what is the impact of IVIG compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 73, we provide indirect evidence from PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) and PICO 40 (IVIG vs no IVIG as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 33 and PICO 40 (no evidence addressing).

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later time points), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.
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For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 33.

Table 73-1. PICO 73: Excluded Studies

References	Reasons for exclusion
Wang et al., 2022 [1]	No comparator of interest
Danieli et al., 2014 [2]	No comparator of interest

References for PICO 73

1. Wang LM, Yang QH, Zhang L, et al. Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Rheumatology (Oxford, England)*.
2. Danieli MG, Gambini S, Pettinari L, Logullo F, Veronesi G, Gabrielli A. Impact of treatment on survival in polymyositis and dermatomyositis. A single-centre long-term follow-up study. *Autoimmunity reviews*. 2014;13(10):1048-54.

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
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PICO 74: In rheumatic disease patients with ILD, what is the impact of oral prednisone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings: 1 observational study reported the following infection rates per 100 person-years:

- 15.4 for prednisone >10 mg/day
- 13.5 for non-TNFI biologics (abatacept or rituximab)
- 11 for prednisone ≤10 mg/day

Summary: 1 observational study addressed this PICO.[1]

No studies directly compared anti-CD20 and oral prednisone as first-line ILD treatment on disease-related outcomes. Zamora-Legoff et al., 2016;[1] however, conducted a retrospective observational cohort study of 181 individuals with RA-ILD and reported adverse events among individuals based upon treatments (see Table 74-1). Rituximab was combined with abatacept as a "non-TNFi biologic," and there were a total of 38 individuals on one of these two treatments (individual treatment numbers of those on rituximab vs. abatacept were not reported). There were 13.5 infections per 100 person-years (py) among those in the "non-TNFi biologic" group. There were 11 infections per 100 py and 15.4 infections per 100 py among individuals taking prednisone ≤10mg/day and >10mg/day, respectively. Prednisone greater than 10 mg (RR 4.40; 95 % CI: 1.38, 27.7) and non-TNFi biologic (RR 3.87; 95 % CI: 1.22, 24.3) had the highest serious infection risk when compared to SSZ/HCQ alone.

Table 74-1: Oral prednisone vs. anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first-line ILD treatment

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Zamora-Legoff et al., 2016[1]	Retrospective observational cohort study	High, observational study	Median follow up time was 3.1 (range 0.01 to 14.8)	181 patients with RA-ILD 87 (48 %) were female and 96 % were Caucasian	Various immunosuppression regimens compared with respect to infection risk Steroid use: ≤10mg/day: n=54 >10mg/day: n=86 Non-TNFi biologic n=38 (abatacept or RTX; did not list individual numbers between these)	Infection rate per 100 person-years Overall (n=181): 7.4 infections per 100 py Pred ≤10mg/day (n=54): 11 infections per 100 py Pred >10mg/day (n=86): 15.4 infections per 100 py Non-TNFi biologic (n=38): 13.5 infections per 100 py MTX/LEF alone (n=54): 7.4 infections per 100 py TNFi (n=59): 1.8 infections per 100 py No therapy (n=48): 6.6 infections per 100 py Prednisone greater than 10 mg (RR 4.40; 95 % CI 1.38, 27.7) and non-TNFi biologic (RR 3.87; 95 % CI 1.22, 24.3) had the highest serious infection risk when compared to SSZ/HCQ alone.

Table 74-2. PICO 74: Excluded Studies

Reference	Reason for Exclusion
Perez-Campos et al., 2012[2]	No comparator of interest
Hozumi et al., 2019[3]	No comparator of interest
Bodolay et al., 2005[4]	No comparator of interest
Friedman et al., 1996[5]	No comparator of interest

Reference	Reason for Exclusion
Chen et al., 2022[6]	No comparator of interest
Adler et al., 2018[7]	No comparator of interest

References

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
2. Perez Campos D, Estevez Del Toro M, Pena Casanovas A, Gonzalez Rojas PP, Morales Sanchez L, Gutierrez Rojas AR. Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis? *Reumatologia clinica*. 2012;8(2):58-62. doi:https://dx.doi.org/10.1016/j.reuma.2011.11.006
3. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
4. Bodolay E, Szekanecz Z, Devenyi K, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology (Oxford, England)*. 2005;44(5):656-61.
5. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Seminars in arthritis and rheumatism*. 1996;26(1):459-67.
6. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
7. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

PICO 75: In rheumatic disease patients with ILD, what is the impact of intravenous methylprednisolone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 75, we provide indirect evidence from PICO 33 (anti-CD20 antibody vs no anti-CD20 antibody as first line ILD treatment) below. No PICO addressed the effectiveness of intravenous methylprednisone as first line ILD treatment. The certainty of evidence across all critical outcomes was rated Very low for PICO 33.

Key Findings from PICO 33: direct evidence from 6 studies (1 RCT, 5 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 33.

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093

2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Korsten P, Rademacher J-G, Riedel L, et al. Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography. *Frontiers in medicine*. 2020;7:609595. doi:https://dx.doi.org/10.3389/fmed.2020.609595
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
5. Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Annals of the rheumatic diseases*. 2015;74(6):1188-94. doi:https://dx.doi.org/10.1136/annrheumdis-2013-204522
6. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum*. 2017;46(5):625-631. DOI: 10.1016/j.semarthrit.2016.10.003.

PICO 76: In rheumatic disease patients with ILD, what is the impact of plasma exchange compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 76, we provide indirect evidence from PICO 41 (plasma exchange vs no plasma exchange as first line ILD treatment) and PICO 33 (anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) vs no anti-CD20 antibody as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for both PICO 33 and PICO 41.

Key Findings from PICO 33: direct evidence from 5 studies (1 RCT, 4 observational studies):

- One small non-blinded non-placebo-controlled randomized trial noted improvements in both FVC and DLCO % predicted in patients already on "standard therapy" who were prescribed rituximab versus no rituximab.
- Four observational studies provided mixed results in comparing rituximab to no rituximab for first-line treatment of CTD-ILD. However, perhaps the best example was a nested case-control study in which rituximab significantly prevented further decline in FVC compared to matched controls, but the analysis was limited to only 18 patients.
- A multicenter open-label trial comparing rituximab to conventional therapy with either MMF, AZA, or MTX demonstrated promising effects of rituximab in treating SSc-ILD, although the open-label study design, ability to be taking concomitant therapies, significant loss to follow-up (particularly at later timepoints), and use of a surrogate outcome (PFT data) limit the utility of these data.

Key Findings from PICO 41: indirect evidence from 1 observational study

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 33 and PICO 41.

Table 76-1. PICO 76: Excluded Studies

Reference	Reason for Exclusion
Tsuji et al., 2020[1]	No comparator of interest

References for PICO 76

1. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105

References for Included Studies for PICO 33

1. Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford, England)*. 2010;49(2):271-80. doi:https://dx.doi.org/10.1093/rheumatology/kep093
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References for Included Studies for PICO 41

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7.

PICO 77: In rheumatic disease patients with ILD, what is the impact of methotrexate compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 77, we provide indirect evidence from PICO 28 (methotrexate vs no methotrexate as first line ILD treatment) and PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 28 and PICO 29.

Key Findings from PICO 28: indirect evidence from 3 observational studies

- 3 observational studies of 381 RA-ILD patients reported that 60 (30.6%) patients classified as "progressive," and 71 (38.3%) patients classified as "stable" were taking methotrexate.
- 1 observational study reported that treatment with MTX, LEF, and tacrolimus were not associated with progression of RA-ILD.
- 1 observational study reported that treatment with MTX was not associated with better survival (HR 0.58, 95% CI: 0.33 to 1.01).

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 28 and PICO 29.

Table 77-1. PICO 77: Excluded Studies

Reference	Reason for Exclusion
Tille-Leblond et al., 2008[1]	No comparator of interest
Fu et al., 2019[2]	No comparator of interest
Chen et al., 2022[3]	No comparator of interest
Zamora-Legoff et al., 2016[4]	No comparator of interest

References for PICO 77

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237
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4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

References for Included Studies for PICO 28

1. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
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References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 78: In rheumatic disease patients with ILD, what is the impact of leflunomide compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 78, we provide indirect evidence from PICO 27 (leflunomide vs no leflunomide as first line ILD treatment) and PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for both PICO 27 and PICO 29.

Key Findings from PICO 27: direct evidence from 2 observational studies:

- One single-center retrospective cohort study assessed the risk of infection of patients receiving methotrexate/leflunomide (n=54) vs. no therapy (n=48). The infection rate in the MTX/LEF group vs. no therapy group was 7.4 vs. 6.6 per 100 person-year (py), respectively.
- A multicenter prospective observational cohort study of RA-ILD patients exposed to either LEF, MTX, or TAC demonstrated that LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, p=0.031 and an increased risk of ILD progression in patients with decreased lung function (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression and were at higher risk for ILD progression.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 27 and PICO 29.

Table 78-1. PICO 78: Excluded Studies

References	Reasons for exclusion
Chen et al., 2022[1]	No comparison of interest
Zamora-Legoff et al., 2016[2]	No comparison of interest

References for PICO 78

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

References for Included Studies for PICO 27

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
2. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
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4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 79: In rheumatic disease patients with ILD, what is the impact of cyclophosphamide compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 79, we provide indirect evidence from PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) and PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Very Low for PICO 29. An additional downgrade due to indirect comparison for PICO 79 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to the treatment benefit of CYC.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.

- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 29.

Table 79-1. PICO 79: Excluded Studies

References	Reasons for exclusion
Ciaffi et al., 2022[1]	No comparison of interest
Chen et al., 2022[2]	No intervention of interest
Kelly et al., 2021[3]	No population of interest
Tsuji et al., 2020[4]	No comparison of interest
Kim et al., 2020[5]	No comparison of interest
Ciaffi et al., 2020[6]	No comparison of interest
Bruni et al., 2020[7]	No comparison of interest
Li et al., 2019[8]	No comparison of interest
Fu et al., 2019[9]	No comparison of interest
Adler et al., 2018[10]	No comparison of interest
Okamoto et al., 2016[11]	No comparison of interest
Kundu et al., 2016[12]	No comparison of interest
Perez-Campos et al., 2012[13]	No comparison of interest
Domiciano et al., 2011[14]	No comparison of interest
Shi et al., 2009[15]	No comparison of interest
Tillie-Leblond et al., 2008[16]	No comparison of interest
Airo et al., 2007[17]	No comparison of interest
Bodolay et al., 2005[18]	No comparison of interest
Davas et al., 1999[19]	No comparison of interest
Grau, et al., 1996[20]	No comparison of interest
Friedman et al., 1996[21]	No comparison of interest

References in PICO 79

1. Ciaffi J, van Leeuwen NM, Boonstra M, et al. Evolution of Systemic Sclerosis-Associated Interstitial Lung Disease One Year After Hematopoietic Stem Cell Transplantation or Cyclophosphamide. *Arthritis care & research*. 2022;74(3):433-441. doi:https://dx.doi.org/10.1002/acr.24451
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4. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
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6. Ciaffi J, van Leeuwen NM, Boonstra M, et al. Evolution of interstitial lung disease one year after hematopoietic stem cell transplantation or cyclophosphamide for systemic sclerosis. *Arthritis care & research*. 2020;doi:https://dx.doi.org/10.1002/acr.24451
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2. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.

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References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
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PICO 80: In rheumatic disease patients with ILD, what is the impact of calcineurin inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Kiboshi et al., 2022[1] found no difference in IMPORTANT outcomes KL-6 levels, %FVC, %DLCO, total GGO score, and total fibrosis score at 12 months follow-up between a very small number (n=18 per group) of individuals in the AZA and TAC groups. The study suggested that the rates of evolution of total fibrosis score, and those corrected by disease duration for 36 months follow-up, were significantly lower in the TAC group than in the AZA group (p=0.017 and 0.025, respectively). However, there was a high dropout rate—39% in the TAC group and 33% in the AZA group.
- Adverse events were reported poorly (CRITICAL outcomes):
    i. Only two patients developed an infection in each group.
    ii. 3 (17%) patients developed mild renal injury at 12 months of follow-up in the TAC group.
    iii. 2 (11%) developed mild leukopenia in the AZA group.
- Chen et al., 2022[2] concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

Summary:

We included two retrospective observational studies.

Kiboshi et al., 2022[1] reported on patients with systemic sclerosis-associated interstitial pneumonia. The study examined treatment outcomes of combination therapy with prednisolone (0.2–0.5 mg/kg/day) accompanied by oral tacrolimus (3 mg/day; n=18) or azathioprine (1–2 mg/kg/day; n=18). Outcomes were assessed at 12- and 36 months of follow-up.

The study also assessed the difference in rates of evolution (in percentage per year) of KL-6 levels, %FVC, %DLCO, total GG score, total fibrosis score, and steroid dose. There were no statistically significant differences except in the total fibrosis score at 36 months of follow-up. The rates of evolution of total fibrosis score (tacrolimus group -2.2 [-5.6 to -0.1] vs. in the azathioprine group 0.6 [-1.6 to 3.2]; p=0.17) and those corrected by disease duration (tacrolimus group -1.3 [-9.1 to -0.1] vs. in the azathioprine group 0.7 [-2.6 to

9.4]; p=0.25) was statistically significantly lower in the tacrolimus group than in the azathioprine group. However, the difference might not be clinically important. There were some imbalances between the groups at the baseline. Participants in the tacrolimus group had higher initial %FVC than those who received azathioprine (82.9% [74.4% to 89.9%] vs. 70.2 [62.3 to 81.5], respectively). Also, the azathioprine group had a lower proportion of women (67% vs. 94%, p=0.04).

Only a few adverse events were reported. In the tacrolimus group, 2 (11%) patients acquired infection at 2 months of follow-up, and 3 (17%) patients developed mild renal injury at 12 months of follow-up. In the AZA group, 2 (11%) patients acquired infection, and 2 (11%) developed mild leukopenia.

Chen et al., 2022[2] concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

Table 80-1. Retrospective Studies that do not provide data that allow quantitatively summarized

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
Kiboshi et al., 2022[1]	Retrospective observational	High	Scleroderma with interstitial pneumonia • 18 pt tacrolimus (TAC) • 18 pt AZA Age (median IQR) Female (%) TAC 64.5 (50.8-70.3) 17 (94%) AZA 69.5 (63-74.5) 12 (67%)	Rates of evolution of the following outcomes in percentage per year: %FVC median (IQR) %DLCO median (IQR), p value GGO score median (IQR), p value Fibrosis score median (IQR), p value Prednisolone dose (PSL) median (IQR), p value Short period (SP): period from initial to 12 months after TAC/AZA initiation; Long period (LP): period from initial to the endpoint	**Rates of evolution for various parameters (in percentage per year) in SSc-PIP patients** ***12 months follow-up*** *(TAC n=18, AZA n=18)**:*** %FVC (IMPORTANT) ***TAC:*** 4.3 (-2.6 to 13.7) ***AZA:*** 2.8 (-1.8 to 15.5) p=0.826 %DLCO (IMPORTANT) ***TAC:*** -5.4(-16.9 to 19.8) ***AZA:*** 13 (-40.4 to -71.8) p=0.925 GGO score (IMPORTANT) ***TAC:*** -35.7(-41.5 to -15.7) ***AZA:*** -29.9 (-47.5 to -13.7) p=0.899

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
					Fibrosis score: (IMPORTANT) ***TAC:*** -17.9 (-22.3 to -5.2) ***AZA:*** -6.0 (-17.2 to 0) p=0.055 PSL dose (NOT IMPORTANT) ***TAC:*** -60 (-80 to -41.7) ***AZA:*** -53.3 (-66.7 to -44.0) p=0.219 ***36 months follow-up (****TAC n=11, AZA n=12):* %FVC (IMPORTANT) ***TAC:*** 0.1 (-1.2 to 3.2) ***AZA:*** 0.8 (-0.3 to 1.4) p=0.472 %DLCO (IMPORTANT) ***TAC:*** 0 (-1.0 to 3.0) ***AZA:*** -0.7 (-4.3 to 3.4) p=0.537 GGO score: (IMPORTANT) ***TAC:*** -8.9 (-10.0 to -4.1) ***AZA:*** -3.9 (-6.5 to -1.1) p=0.062 Fibrosis score: (IMPORTANT) ***TAC:*** -2.2 (-5.6 to -0.1) ***AZA:*** 0.6 (-1.6 to 3.2 p=0.017 PSL dose (NOT IMPORTANT) ***TAC:*** -15.3 (-22.0 to -10.5) ***AZA:*** -10.2 (-17.8 to -6.7) p=0.085

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
					Rates of evolution for various parameters (in percentage per year) corrected by disease duration in SSc-PIP patients ***12 months follow-up*** *(TAC n=18, AZA n=18)**:*** %FVC (IMPORTANT) ***TAC:*** 1.7 (-1.4 to 57.8) ***AZA:*** 4.9 (-3.5 to 18.7) p=0.875 %DLCO (IMPORTANT) ***TAC:*** -2.1 (-14.5 to 56.3) ***AZA:*** 10.2 (-86.8 to 136.8) p=0.729 GGO score: (IMPORTANT) ***TAC:*** -31.7 (-120.1 to -5.9) ***AZA:*** -61 (-240.0 to -25.1) p=0.303 Fibrosis score: (IMPORTANT) ***TAC:*** -14.8 (-79.8 to -2.1) ***AZA:*** -11.5 (-30.0 to 0) p=0.394 PSL dose (NOT IMPORTANT) ***TAC:*** -73.8 (-260.0 to -11.1) ***AZA:*** -102.9 (-264.0 to -40.0) p=0.546 ***36 months follow-up (****TAC n=11, AZA n=12**)**:*** %FVC (IMPORTANT) ***TAC:*** 0.2 (-1.2 to 8.4) ***AZA:*** 0.5 (-0.9 to 8.1) p=0.829

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
					%DLCO (IMPORTANT) ***TAC:*** 0 (-2.7 to 1.3) ***AZA:*** -0.5 (-7.4 to 15.9) p=0.758 GGO score: (IMPORTANT) ***TAC:*** -8.2 (-48.7 to -1.9) ***AZA:*** -5.2 (23.5 to -1.1) p=0.836 Fibrosis score: (IMPORTANT) ***TAC:*** -1.3 (-9.1 to -0.1) ***AZA:*** 0.7 (-2.6 to 9.4) p=0.025 PSL dose (NOT IMPORTANT) ***TAC:*** -17.6 (-56.5 to -2.7) ***AZA:*** -28.2 (-89.8 to -6.4) p=0.790 **Adverse Events** (CRITICAL) Only a few adverse events were reported. In the tacrolimus group, 2 (11%) patients acquired infection at 2 months of follow-up, 3 (17%) patients developed mild renal injury at 12 months of follow-up. In the AZA group, 2 (11%) patients acquired infection and 2(11%) developed mild leukopenia

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
Chen et al., 2022[2]	Retrospective cohort study	High	A total of 250 patients with idiopathic inflammatory myopathies-associated interstitial lung disease (IIM-ILD)	Retrospective study: Tacrolimus group (n=93), Conventional therapy group (n=157). In the conventional therapy group, cyclophosphamide (CTX) was the most frequently used immunosuppressive agent, followed by methotrexate (MTX) and azathioprine (AZA).	Compared to AZA, the 12-month survival rate was significantly improved by tacrolimus. Tacrolimus was superior in reducing the mortality rate and recurrence rate of IIM-ILD within the first year of treatment compared with other conventional immunosuppressive agents.

AZA: azathioprine; **DLCO:** diffusing capacity of the lung for carbon monoxide; **FVC:** forced vital capacity; **GGO:** ground glass opacities; **IQR**: interquartile range; **LP:** long period; **PSL**: prednisolone; **SP**: short period; **SSc:** systemic sclerosis; **TAC**: tacrolimus

Table 80-2. PICO 80: Excluded Studies

References	Reasons for exclusion
Hozumi et al., 2019[3]	No comparison of interest
Takada et al., 2020[4]	No comparison of interest
Tsuji et al., 2020[5]	No comparison of interest
Okamoto et al., 2016[6]	No comparison of interest

References for PICO 80

1. Kiboshi T, Kotani T, Konma J, et al. Comparison of therapeutic effects of combination therapy with prednisolone and tacrolimus or azathioprine on progressive interstitial pneumonia with systemic sclerosis. *Modern rheumatology*. 2022;32(2):358-364. doi:https://dx.doi.org/10.1080/14397595.2021.1918864
2. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. Frontiers in immunology. 2022;13:978429.
3. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
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5. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
6. Okamoto M, Fujimoto K, Sadohara J, et al. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. *Respiratory Investigation*. 2016;54(6):445-453. doi:https://dx.doi.org/10.1016/j.resinv.2016.05.004

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

References for Included Studies for PICO 30

1. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases complicated with dermatomyositis: A retrospective analysis. *Medicine*. 2022;101(24):e29108. doi:https://dx.doi.org/10.1097/MD.0000000000029108
2. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105
3. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
4. Kurita T, Yasuda S, Oba K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology (Oxford, England)*. 2015;54(1):39-44. doi:https://dx.doi.org/10.1093/rheumatology/keu166
5. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

PICO 81: In rheumatic disease patients with ILD, what is the impact of TNF inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings: Indirect evidence from 2 observational studies indicated:

- An adjusted mortality rate ratio of 0.81, 95% CI: 0.38 to 1.73 for the TNFi RA-ILD cohort vs. the csDMARD RA-ILD cohort (based on data from the British Society for Rheumatology Biologics Register [BSRBR])[1]
- No significant difference between RA-ILD patients on TNFis that were categorized as progressive RA-ILD (15.6%) vs stable RA-ILD (34.9%).[2]

Summary: 2 observational studies addressed this PICO.[1,2]

Although there were no studies identified that made a head-to-head comparison of outcomes between TNFi and azathioprine, Dixon et al., 2010[1] examined the influence of anti-TNF therapy on all-cause and ILD- specific mortality in patients with pre-existing RA-ILD. The subjects for this analysis were participating in a large national prospective observational study, the British Society for Rheumatology Biologics Register (BSRBR). Analysis was restricted to patients registered with the BSRBR with a physician diagnosis of RA who were commencing an anti-TNF drug as their first biological drug. The cohort of biologic-naïve patients with active RA was recruited in parallel and was the comparator group - how many if any of these patients were receiving azathioprine was not reported. Study period: 2001-2008.

A total of 13 883 patients were included in the analyses, 3464 in the csDMARD cohort, and 10,649 patients had ever received an anti-TNF drug; 210 patients switched from the csDMARD cohort to the anti-TNF cohort and contributed person-years to both cohorts. Fourteen of 68 (21%) of the csDMARD RA-ILD cohort died during this follow-up period compared with 70 of 299 (23%) of the anti-TNF RA-ILD cohort (see Table 81-1). After full adjustment for potential confounders, the adjusted mortality rate-ratio fell to 0.81 (0.38 to 1.73).

A study by Chen et al., 2022[2] evaluated the rate of RA-ILD progression in their cohort of patients with RA-ILD and found that the proportion of patients on TNFi that progressed vs. remained stable were similar between the 2 groups: 5/32 progressed (15.6%) vs 15/43 were stable (34.9%); p=0.06 (see Table 81-2).

Table 81-1. PICO 81: TNF inhibitors vs csDMARD for first line ILD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	csDMARD	Relative (95% CI)	Absolute (95% CI)		
Mortality												
Dixon et al., 2010[1]	observational studies	serious[a]	not serious	serious[b]	serious[c]		70/299 (23.4%)	14/68 (20.6%)	**RR 1.14 (0.68 to 1.89)**	**29 more per 1,000 (from 66 fewer to 183 more)**	⊕◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

- **a.** retrospective, no randomization or blinding
- **b.** indirect comparison
- **c.** 95% CI includes the possibility of no difference

Table 81-2. TNF inhibitors vs azathioprine as first line ILD

Author, year	Study	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Chen et al., 2022[2]	Retrospective cohort study	High	Pulmonary functional impairment compared with the diagnosis of baseline time, assessed by changes of HRCT score or PFT during follow-up	RA-ILD patients seen at Changhai Hospital, divided into the "progressive group" (*n*=32) and the "stable group" (*n*=43)	Univariate Cox survival analyses performed to determine whether certain demographic covariates, lab data, PFT data, or CT pattern associated with "progressive" disease Steroids, LEF, MTX, CYC/MMF, TNFi	Among the progressive RA-ILD group, 5/32 (15.6%) were on TNFi and among the stable group, 15/43 (34.9%) were taking TNFi; p=0.06.

Table 81-3. PICO 81: Excluded Studies

Reference	Reason for Exclusion
Zamora-Legoff et al., 2016[3]	Not a comparator of interest

References

1. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Annals of the rheumatic diseases*. 2010;69(6):1086-91. doi:https://dx.doi.org/10.1136/ard.2009.120626
2. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
3. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

PICO 82: In rheumatic disease patients with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 82, we provide indirect evidence from PICO 34 (IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment) and PICO 29 (azathioprine compared to no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 34 and Very Low for PICO 29. An additional downgrade due to indirect comparison for PICO 82 resulted in a rating of Very low (for IL-6 receptor antagonists) and Very Low (for azathioprine).

Key Findings from PICO 34: indirect evidence from 4 studies (2 RCTs, and 2 observational studies):

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.
- The aforementioned study's preceding phase 2 randomized controlled trial demonstrated slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a post hoc analysis of the aforementioned RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.
- One observational study of SSc patients reported no difference for FVC% predicted with tocilizumab vs without tocilizumab at 12 months.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 29 and PICO 34.

Table 82-1. PICO 82: Excluded Studies

Reference	Reason for Exclusion
Suleman et al., 2021[1]	Wrong study design

References for PICO 82

1. Suleman Y, Clark KEN, Cole AR, Ong VH, Denton CP. Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase-positive patients. *Rheumatology (Oxford, England)*. 2021;60(8):3945-3946.

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461

3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

References for Included Studies for PICO 34

1. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2020;8(10):963-974. doi:https://dx.doi.org/10.1016/S2213-2600(20)30318-0
2. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630-2640. DOI: 10.1016/s0140-6736(16)00232-4.
3. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(7):1301-1310. doi:https://dx.doi.org/10.1002/art.41668
4. Kuster S, Jordan S, Elhai M, et al. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD open. 2022;8(2)

PICO 83: In rheumatic disease patients with ILD, what is the impact of abatacept compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 83, we provide indirect evidence from PICO 32 (abatacept compared to no abatacept as first line ILD treatment) and PICO 29 (azathioprine compared to no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for both PICO 32 and PICO 29.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 32: indirect evidence from 3 observational studies

- One retrospective study without a comparator group evaluated 16 RA-ILD patients who received abatacept for at least one year. No patients had a worsening in ILD severity during the study period.
- In one small retrospective study that included 44 patients who received abatacept and 31 patients who received a JAKi, there was no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.
- Although the differences were small, one retrospective study of RA-ILD patients demonstrated that receiving abatacept vs any form of TNFi may be associated with a decreased risk of ILD exacerbation or serious respiratory complications.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 29 and PICO 32.

Table 83-1. PICO 83: Excluded Studies

Reference	Reason for Exclusion
Nakashita et al., 2016[1]	Wrong study design
Tardella et al., 2022[2]	No intervention of interest
Kang et al., 2020[3]	No intervention of interest

References for PICO 83

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9. doi:https://dx.doi.org/10.1016/j.resinv.2016.03.001
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408. doi:https://dx.doi.org/10.1016/j.semarthrit.2019.11.010

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

References for Included Studies for PICO 32

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9. doi:https://dx.doi.org/10.1016/j.resinv.2016.03.001
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w
3. Kang EH, Jin Y, Desai RJ, Liu J, Sparks JA, Kim SC. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Seminars in arthritis and rheumatism*. 2020;50(3):401-408. doi:https://dx.doi.org/10.1016/j.semarthrit.2019.11.010

PICO 84: In rheumatic disease patients with ILD, what is the impact of JAK inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5-associated ILD.[1]
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.[2]

Summary: 2 observational studies indirectly addressed this PICO.

One retrospective study (Fan et al. 2022[1] compared outcomes for MDA5-ILD patients who received tofacitinib (n=26) vs those who received tacrolimus (TAC)(n=35). The 6-month (38.5% vs 62.9%; P = 0.03) and 1-year (44.0% vs 65.7%; P = 0.03) mortality rates in the TOF group were significantly lower than those in the TAC group. Although more patients in the TAC group experienced RP-ILD (22 vs 13), the mortality rates for the TOF group were lower than the TAC group for patients with RP-ILD (76.9% vs 95.5%, P = 0.02 at six months; 84.6% vs 100.0%, p= 0.02 at one year).

In a study by Tardella et al. 2022,[2] 31 RA-ILD patients who received a JAKi and 44 patients who received abatacept were retrospectively studied using a computer-aided method (CaM) to assess changes in (HRCT) fibrosis percentage. Patients were classified as worsened (15% more fibrosis), stable, or improved (15% less fibrosis). After 18 months, 5 (11.4%) patients showed a HRCT deterioration, 32 (72.6%) were considered stable, and 7 (16.0%) patients showed an HRCT improvement in the ABA group. In the JAKis group 5 (16.1%) patients showed a HRCT deterioration, 20 (64.5%) were considered stable, and 6 (19.4%) patients showed an HRCT improvement. There was no significant change in mean FVC, DLCO, or CT fibrosis scores. Abatacept was not first-line treatment for this study and patients concomitantly taking methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs) and/or glucocorticoids at a dose of less than 10 mg daily prednisone or equivalent were included.

Table 84-1: impact of JAK inhibitors vs no JAK inhibitors as first line ILD treatment

Author, year	Study design	Risk of bias	Time of reassessment	Population Description	Screening or assessment measures	Results
Fan et al. 2022 [1]	Retrospective observational study	High		MDA5-ILD patients treated with either Tofacitinib or TAC	26 patients were treated with TOF and 35 were treated with TAC	Entire group TOF TAC 6-month mortality 10 (38.5%) 22 (62.9%) P=0.03 1-year mortality 11 (44.0%) 23 (65.7%) p=0.03 RP-ILD TOF TAC 6-month mortality 10 (76.9%) 21 (95.5%) p=0.02 1-year mortality 11 (84.6%) 22 (100%) p=0.02
Tardella et al. 2022[2]	Retrospective observational study	High		75 RA-ILD patients who received either JAKis or abatacept. Seventy-five patients (69.3% women) were evaluated, 31 received a JAKi while 44 received ABA.	31 patients who received a JAKi and 44 patients who received Abatacept. Computer-aided method (CaM) used to assess changes in (HRCT) fibrosis percentage and classify patients as worsened (15% more), stable, or improved (15% less) fibrosis after 18 months.	Abatacept JAKis Time 0 Time 18 Time 0 Time 18 DLCO 58.69 61.36 59.72 62.77 FVC 82.29 81.24 81.18 79.59 HRCTcam 19.41 18.94 18.54 17.52 All p values NS CT deterioration Stability Improved ABA 5 (11.4%) 32 (72.6%) 7 (16%) JAKis 5 (16%) 20 (65.5%) 6 (19.4%)

PICO 85: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low to Very low**

Due to the lack of direct evidence for PICO 85, we provide indirect evidence from PICO 38 (nintedanib compared to no nintedanib as first line ILD treatment) and PICO 29 (azathioprine compared to no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Moderate to Low for PICO 38 and Very Low for PICO 29. An additional downgrade due to indirect comparison for PICO 85 resulted in a rating of Low (for nintedanib) to Very Low (for azathioprine).

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.
    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).

- In both RCTs (SENSCIS, INBUILD) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS, INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 38 and PICO 29.

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076
2. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681

4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020
5. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1
6. Assassi S, Distler O, Allanore Y, et al. Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial. *ACR Open Rheumatology*. 2022;doi:https://dx.doi.org/10.1002/acr2.11483
7. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. *Annals of the rheumatic diseases*. 2020;79(11):1478-1484. doi:https://dx.doi.org/10.1136/annrheumdis-2020-217331
8. Volkmann ER, Kreuter M, Hoffmann-Vold AM, et al. Dyspnoea and cough in patients with systemic sclerosis-associated interstitial lung disease in the SENSCIS trial. *Rheumatology (Oxford, England)*. 2022;doi:https://dx.doi.org/10.1093/rheumatology/keac091
9. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
10. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory investigation*. 2021;59(2):252-259. doi:https://dx.doi.org/10.1016/j.resinv.2020.10.005
11. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402
12. Maher TM, Mayes MD, Kreuter M, et al. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(4):671-676. doi:https://dx.doi.org/10.1002/art.41576

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.

2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 86: In rheumatic disease patients with ILD, what is the impact of pirfenidone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the limited evidence for PICO 86, we provide indirect evidence from PICO 39 (pirfenidone compared to no pirfenidone as first line ILD treatment) and PICO 29 (azathioprine compared to no azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated as Low for PICO 39 and Very low for both PICO 29. An additional downgrade for indirect comparison for PICO 86 resulted in a rating of Very low.

Key Findings from PICO 86:

- Chen et al. 2022 concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

Summary: One retrospective observational study (Chen et al. 2022[1]) examining 250 patients with idiopathic inflammatory myopathies-associated interstitial lung disease (IIM-ILD), concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus (see Table 86-1 below).

Key Findings from PICO 39: direct evidence from 3 RCTs

- One double-blind RCT (n=29) reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- One phase 2 RCT (TRAIL1) (n=123) reported no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). In addition, hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.
- One double-blind, phase 2b RCT (RELIEF) (n=127) reported significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo. This study was prematurely terminated based on an interim analysis for futility triggered by slow recruitment, resulting in missed values and many patients not completing treatment as intended.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit

the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.

- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 39 and PICO 29.

Table 86-1. Retrospective studies that do not provide data that allow quantitative summarization

Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
Chen et al., 2022[1]	Retrospective cohort study	High	A total of 250 patients with idiopathic inflammatory myopathies-associated interstitial lung disease (IIM-ILD)	Retrospective study: Tacrolimus group (n=93), Conventional therapy group (n=157). In the conventional therapy group, cyclophosphamide (CTX) was the most frequently used immunosuppressive agent, followed by methotrexate (MTX) and azathioprine (AZA).	Compared to AZA, the 12-month survival rate was significantly improved by tacrolimus.

Table 86-2. PICO 86: Excluded Studies

Reference	Reason for Exclusion
Li et al., 2016[2]	No intervention or comparator of interest

References for PICO 86

1. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. Frontiers in immunology. 2022;13:978429.

2. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Scientific reports*. 2016;6:33226. doi:https://dx.doi.org/10.1038/srep33226

References for Included Studies for PICO 39

1. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology international*. 2020;40(5):703-710. doi:https://dx.doi.org/10.1007/s00296-020-04565-w
2. Solomon JJ, Danoff S, Woodhead F, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease. *medRxiv*. 2022;doi:https://dx.doi.org/10.1101/2022.04.01.22273270
3. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory medicine*. 2021;9(5):476-486. doi:https://dx.doi.org/10.1016/S2213-2600(20)30554-3

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 87: In rheumatic disease patients with ILD, what is the impact of IVIG compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 87, we provide indirect evidence from PICO 29 (azathioprine compared to no azathioprine as first line ILD treatment) and PICO 40 (IVIG compared to no IVIG as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated as Very Low for both PICO 29 and PICO 40 (no studies addressing).

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 29.

Table 87-1. PICO 87: Excluded Studies

Reference	Reason for Exclusion
Danieli et al., 2014[1]	No comparator of interest
Wang et al., 2022[2]	No population of interest

References for PICO 87

1. Danieli MG, Gambini S, Pettinari L, Logullo F, Veronesi G, Gabrielli A. Impact of treatment on survival in polymyositis and dermatomyositis. A single-centre long-term follow-up study. *Autoimmunity reviews*. 2014;13(10):1048-54. doi:https://dx.doi.org/10.1016/j.autrev.2014.08.023
2. Wang LM, Yang QH, Zhang L, et al. Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Rheumatology (Oxford, England)*. 2021;doi:https://dx.doi.org/10.1093/rheumatology/keab928

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 88: In rheumatic disease patients with ILD, what is the impact of oral prednisone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 88, we provide indirect evidence from PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) and PICO 36 (daily oral prednisone vs no daily oral prednisone as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 29 and PICO 36 (no evidence addressing).

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summary and data provided in Summary of Findings (SOF)/Word tables under PICO 29.

Table 88-1. PICO 88: Excluded Studies

Reference	Reason for Exclusion
Perez-Campos et al., 2012[1]	No comparator of interest
Hozumi et al., 2019[2]	No comparator of interest
Bodolay et al., 2005[3]	No comparator of interest
Friedman et al., 1996[4]	Wrong study design
Chen et al., 2022[5]	No intervention of interest
Zamora-Legoff et al., 2016[6]	No intervention of interest
Adler et al., 2018[7]	No comparator of interest

References for PICO 88

1. Perez Campos D, Estevez Del Toro M, Pena Casanovas A, Gonzalez Rojas PP, Morales Sanchez L, Gutierrez Rojas AR. Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis? *Reumatologia clinica*. 2012;8(2):58-62. doi:https://dx.doi.org/10.1016/j.reuma.2011.11.006
2. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
3. Bodolay E, Szekanecz Z, Devenyi K, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology (Oxford, England)*. 2005;44(5):656-61.
4. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Seminars in arthritis and rheumatism*. 1996;26(1):459-67.
5. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
6. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
7. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043

4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 89: In rheumatic disease patients with ILD, what is the impact of intravenous methylprednisolone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 89, we provide indirect evidence from PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) below. No PICO addressed the effectiveness of intravenous methylprednisone as first line ILD treatment. The certainty of evidence across all critical outcomes was rated Very low for PICO 29.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that among patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 29.

Table 89-1. PICO 89: Excluded Studies

Reference	Reason for exclusion
Chen et al., 2022[1]	Not a comparator of interest

References for PICO 89

1. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. *Frontiers in immunology*. 2022;13:978429. doi:https://protect-us.mimecast.com/s/Ri1ZCOYZ1KHp6XZ3UrQdkK-?domain=dx.doi.org

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 90: In rheumatic disease patients with ILD, what is the impact of plasma exchange compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 90, we provide indirect evidence from PICO 29 (azathioprine vs no azathioprine as first line ILD treatment) and PICO 41 (plasma exchange vs no plasma exchange as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for both PICO 29 and PICO 41.

Key Findings from PICO 29: indirect evidence from 4 studies (1 RCT and 3 observational)

- In one RCT, there was a trend towards a slower rate of decline in FVC % predicted in patients receiving a combination of prednisolone, CYC, and AZA compared to placebo, although small sample sizes and significant loss to follow-up largely limit the quality of evidence. In addition, because the intervention described is a combination of multiple therapies, the study does not directly address PICO 29.
- Two observational studies did not demonstrate a benefit in AZA for treating CTD-ILD. However, one study of pSS-ILD had an extremely limited sample size and the other allowed patients to be on other therapies not directly specified, thus limiting their utility in answering PICO 29.
- One observational study indicated that of patients taking AZA, MMF, and RTX, the FVC% predicted was highest for MMF, while DLCO% predicted was highest for RTX.

Key Findings from PICO 41: indirect evidence from 1 observational study

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 29 and PICO 41.

Table 90-1. PICO 90: Excluded Studies

Reference	Reason for Exclusion
Tsuji et al., 2020[1]	No intervention of interest

References for PICO 90

1. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105

References for Included Studies for PICO 29

1. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
2. Amlani B, Elsayed G, Barvalia U, et al. Treatment of primary sjogren's syndrome-related interstitial lung disease: a retrospective cohort study. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG*. 2020;37(2):136-147. doi:https://dx.doi.org/10.36141/svdld.v37i2.8461
3. Kaenmuang P, Navasakulpong A. Short-Term lung function changes and predictors of progressive systemic sclerosis-Related interstitial lung disease. *Tuberculosis and Respiratory Diseases*. 2020;83(4):312-320. doi:https://dx.doi.org/10.4046/TRD.2020.0043
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

References for Included Studies for PICO 41

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7.

PICO 91: In rheumatic disease patients with ILD, what is the impact of methotrexate compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings: Indirect evidence from 1 observational study[1] included:

- 28 (27.1%) patients classified as "progressive" and 32 (39.5%) patients classified as "stable" were taking methotrexate (p=0.08), while 38 (36.8%) patients classified as "progressive", and 43 (53.1%) patients classified as "stable" were taking cyclophosphamide (p=0.04).
- Treatment with cyclophosphamide was associated with better survival (HR 0.43, 95% CI: 0.26 to 0.69; p<0.01).

Summary:

Evidence for ILD progression was provided by Fu et al., 2019[1], a retrospective cohort study in China conducted from May 2008 to January 2014 (n=266). The outcomes of interest were 1) ILD progression defined as: a decrease of FVC > 10% or DLCO > 15% predicted, worsening of ILD or death from respiratory failure due to ILD and/or pneumonia; and 2) survival. The median observation period was 51.02 months (range 2.66–104.79 months).

The 3-year survival rate was 81.24%, and the 5-year survival rate was 69.71%. During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. 103 RA-ILD patients experienced ILD progression, and 81 were stable. 28 (27.1%) patients classified as "progressive" and 32 (39.5%) patients classified as "stable" were taking methotrexate (p=0.08), while 38 (36.8%) patients classified as "progressive," and 43 (53.1%) patients classified as "stable" were taking cyclophosphamide (p=0.04) (see Table 91-1). Treatment with cyclophosphamide was associated with better survival (HR: 0.43, 95% CI: 0.26–0.69, p< 0.01) (see Table 91-2).

Table 91-1: PICO 91: Methotrexate vs. cyclophosphamide as first-line ILD treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Progressive RA-ILD	Stable RA-ILD	Relative (95% CI)	Absolute (95% CI)		
MTX use (patients classified as progressive vs stable)												
1 Fu et al., 2019[1]	observational studies	serious[a]	not serious	serious[b]	Serious[c,d]		28/103 (27.2%)	32/81 (39.5%)	**RR 0.69 (0.45 to 1.04)**	**122 fewer per 1,000 (from 217 fewer to 16 more)**	⨁◯◯◯ Very low	Important
CYC use (patients classified as progressive vs stable)												
1 Fu et al., 2019[1]	observational studies	serious[a]	not serious	serious[b]	Serious[c,d]		38/103 (36.9%)	43/81 (53.1%)	**RR 0.69 (0.50 to 0.96)**	**165 fewer per 1,000 (from 265 fewer to 21 fewer)**	⨁◯◯◯ Very low	Important

CI: confidence interval; **RR:** risk ratio

Explanations

a. retrospective, no randomization or blinding
b. indirect comparison of treatments
c. single study, 95% CI includes the line of no difference
d. single study

Table 91-2: PICO 91: Methotrexate vs. cyclophosphamide as first-line ILD treatment

Author, Study	Study	Risk of Bias	Follow-up	Population description	Treatment comparator	Results
Fu et al., 2019[1]	Retrospective cohort study, single center RA-ILD	High	Median FU 51.02 months (2.66-104.79)	266 patients, 61% female, mean age 64.8 y, 68% older than 60 years of age. 82% with ILD with Ra preceding ILD onset. UIP pattern 37.22, NSIP 26%; Interobserver agreement between radiologist moderate kappa statistic 0.46 4. 14 pts. Used biologic agents (10 biosimilar anti-TNF, 2 with adalimumab and 2 with infliximab).	Treatments: cyclophosphamide, methotrexate	Baseline clinical characteristics of RA-ILD patients with lung progression vs stable lungs were: cyclophosphamide 38/103 (36.8%) vs 43/81 (53.1%); p=0.04 methotrexate: 28/103 (27.1%) 32/81 (39.5%); p=0.08 (see Table 91-1) During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. In multivariable Cox regression analyses, the HR for MTX use with survival was 0.58 (0.33-1.01). Cox hazards modeling revealed that treatment with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, P < 0.01) was associated with better survival.

Table 91-3. PICO 91: Excluded Studies

Reference	Reason for Exclusion
Tillie-Leblond et al., 2008[2]	Wrong study design
Chen et al., 2022[3]	No comparator of interest
Zamora-Legoff et al., 2016[4]	No comparator of interest

References

1. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
2. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

3. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

PICO 92: In rheumatic disease patients with ILD, what is the impact of leflunomide compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 92, we provide indirect evidence from PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) and PICO 27 (leflunomide vs no leflunomide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Very low for PICO 27. An additional downgrade due to indirect comparison for PICO 92 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results regarding the treatment benefit of CYC.

Key Findings from PICO 27: direct evidence from 2 observational studies:

- One single-center retrospective cohort study assessed the risk of infection of patients receiving methotrexate/leflunomide (n=54) vs. no therapy (n=48). The infection rate in the MTX/LEF group vs. no therapy group was 7.4 vs. 6.6 per 100 person-year (py), respectively.
- A multicenter prospective observational cohort study of RA-ILD patients exposed to either LEF, MTX, or TAC demonstrated that LEF exposure was associated with a shorter time to ILD progression (29.4 vs 43 months; log-rank, $p=0.031$ and an increased risk of ILD progression in patients with decreased lung function (adjusted HR, 8.42; 95% CI, 2.61, 27.15). MTX users who were exposed to LEF showed shorter times to ILD progression and were at higher risk for ILD progression.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 27.

Table 92-1. PICO 92: Excluded Studies

Reference	Reason for Exclusion
Chen et al., 2022[1]	Not a comparator of interest
Zamora-Legoff et al., 2016[2]	Not a comparator of interest

References for PICO 92

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

References for Included Studies for PICO 26

1. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *The New England journal of medicine.* 2006;354(25):2655-66.
2. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
3. Jensen ML, Lokke A, Hilberg O, Hyldgaard C, Bendstrup E, Tran D. Clinical characteristics and outcome in patients with antisynthetase syndrome associated interstitial lung disease: a retrospective cohort study. *European clinical respiratory journal*. 2019;6(1):1583516. doi:https://dx.doi.org/10.1080/20018525.2019.1583516
4. Tzelepis GE, Plastiras SC, Karadimitrakis SP, Vlachoyiannopoulos PG. Determinants of pulmonary function improvement in patients with scleroderma and interstitial lung disease. *Clinical and experimental rheumatology*. 2007;25(5):734-9.
5. Nakamura K, Ohbe H, Ikeda K, et al. Intravenous cyclophosphamide in acute exacerbation of rheumatoid arthritis-related interstitial lung disease: A propensity-matched analysis using a nationwide inpatient database. *Seminars in arthritis and rheumatism*. 2021;51(5):977-982. doi:https://dx.doi.org/10.1016/j.semarthrit.2021.07.008

6. Adler S, Huscher D, Siegert E, et al. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. *Arthritis research & therapy*. 2018;20(1):17. doi:https://dx.doi.org/10.1186/s13075-018-1517-z
7. Steen VD, Lanz JK, Jr C, C O, G. R M, T. A, Jr. Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. *Arthritis and rheumatism*. 1994;37(9):1290-6.
8. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
9. Furst DE, Tseng C-H, Clements PJ, et al. Adverse events during the Scleroderma Lung Study. *The American journal of medicine*. 2011;124(5):459-67. doi:https://dx.doi.org/10.1016/j.amjmed.2010.12.009
10. Clements PJ, Roth MD, Elashoff R, et al. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. *Annals of the rheumatic diseases*. 2007;66(12):1641-7.
11. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *American journal of respiratory and critical care medicine*. 2008;177(1):91-8.
12. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *American journal of respiratory and critical care medicine*. 2007;176(10):1026-34.
13. Theodore AC, Tseng C-H, Li N, Elashoff RM, Tashkin DP. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: *findings from the Scleroderma Lung Study*. Chest. 2012;142(3):614-621. doi:https://dx.doi.org/10.1378/chest.11-0801
14. Goldin J, Elashoff R, Kim HJ, et al. Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: *findings from the scleroderma lung study*. Chest. 2009;136(5):1333-1340. doi:https://dx.doi.org/10.1378/chest.09-0108
15. Kim HJ, Brown MS, Elashoff R, et al. Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. *European radiology*. 2011;21(12):2455-65. doi:https://dx.doi.org/10.1007/s00330-011-2223-2
16. Sindhwani G, Shirazi N, Sodhi R, Raghuvanshi S, Rawat J. Transbronchial lung biopsy in patients with diffuse parenchymal lung disease without 'idiopathic pulmonary fibrosis pattern' on HRCT scan - Experience from a tertiary care center of North India. *Lung India*. 2015;32(5):453-456. doi:https://dx.doi.org/10.4103/0970-2113.164148
17. Kim HJ, Tashkin DP, Gjertson DW, et al. Transitions to different patterns of interstitial lung disease in scleroderma with and without treatment. *Annals of the rheumatic diseases*. 2016;75(7):1367-71. doi:https://dx.doi.org/10.1136/annrheumdis-2015-208929

References for Included Studies for PICO 27

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
2. Kim J-W, Chung SW, Pyo JY, et al. Methotrexate, leflunomide, and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. *Rheumatology (Oxford, England)*. 2022;doi:https://protect-us.mimecast.com/s/1rCMCjRnG1Hn7JGgIYX2a9S?domain=dx.doi.org

PICO 93: In rheumatic disease patients with ILD, what is the impact of calcineurin inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings: One observational study examining tacrolimus vs conventional treatment reported a significant improvement in 12- the month survival rate and a significantly lower relapse rate with tacrolimus.

Summary: One study (Chen et al., 2022[1]), indirectly addressing this PICO, compared a combination of tacrolimus with glucocorticoids to a conventional treatment, represented by either cyclophosphamide (CTX), which was the most frequently used immunosuppressive agent, or methotrexate (MTX) and azathioprine (AZA). This study concluded that there was a significant improvement in the 12-month survival rate after adjustment in the tacrolimus group compared to the conventional treatment group and a lower relapse rate (38.7% in TAC vs 51.6% in the conventional group). Tacrolimus was superior in reducing mortality and recurrence rates.

Table 93-2. PICO 93: Included Studies

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Treatments	Results
Chen et al., 2022[1]	Retrospective cohort study	High	A total of 250 patients consisting of 93 patients treated with tacrolimus and 157 patients received other conventional therapies were consecutively enrolled in the retrospective study.	Tacrolimus group (n=93), Conventional therapy group (n=157). Oral tacrolimus was given twice daily (0.075 mg/kg of body weight) to achieve a plasma trough level of 5–10 ng/ml. In the conventional therapy group, cyclophosphamide (CTX) was the most frequently used immunosuppressive agent, followed by methotrexate (MTX) and azathioprine (AZA).	A significant improvement in **12-month survival rate** after adjustment was observed in tacrolimus group compared to conventional treatment group (log-rank p =0.0029, weighted HR=0.33; 95% CI:0.161-0.675, P=0.002). **Relapse events**: 39 patients (38.7%) in tacrolimus group and 81 patients (51.6%) in conventional therapy group. After adjustment, the tacrolimus group showed a significantly lower relapse rate compared with the conventional therapy group (log-rank p=0.0038, weighted HR=0.548, 95% CI: 0.368-0.816, P=0.003). **Mortality and recurrence**: Tacrolimus was superior in reducing the mortality rate and recurrence rate of IIM-ILD within the first year of

					treatment compared with other conventional immunosuppressive agents.

Note: Two other questions targeted the comparative effectiveness of azathioprine and cyclophosphamide (PICO 156 [Rheumatic disease with ILD progression after any 1st ILD therapy] and PICO 224 [Rheumatic disease with rapidly progressive ILD]). None of these questions identified eligible studies.

Table 93-1. PICO 93: Excluded Studies

Reference	Reason for Exclusion
Hozumi et al., 2019[2]	No intervention of interest
Takada et al., 2020[3]	No comparator of interest
Ingegnoli et al., 2012[4]	No outcome of interest
Tsuji et al., 2020[5]	Wrong study design
Okamoto et al., 2016[6]	Wrong study design
Nakazawa et al., 2018[7]	Wrong study design

References

1. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. Frontiers in immunology. 2022;13:978429. doi:https://protect-us.mimecast.com/s/Ri1ZCOYZ1KHp6XZ3UrQdkK-?domain=dx.doi.org
2. Hozumi H, Fujisawa T, Nakashima R, et al. Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody-positive Polymyositis/dermatomyositis-associated Interstitial Lung Disease: A Propensity Score-matched Analysis. *The Journal of rheumatology*. 2019;46(5):509-517. doi:https://dx.doi.org/10.3899/jrheum.180778
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6. Okamoto M, Fujimoto K, Sadohara J, et al. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. *Respiratory Investigation*. 2016;54(6):445-453. doi:https://dx.doi.org/10.1016/j.resinv.2016.05.004
7. Nakazawa M, Kaneko Y, Takeuchi T. Risk factors for the recurrence of interstitial lung disease in patients with polymyositis and dermatomyositis: a retrospective cohort study. *Clinical rheumatology*. 2018;37(3):765-771. doi:https://dx.doi.org/10.1007/s10067-017-3854-8
8.

PICO 94: In rheumatic disease patients with ILD, what is the impact of TNF inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 94, we provide indirect evidence from PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) and PICO 31 (anti-TNF therapy vs no anti-TNF therapy as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Very low for PICO 31. An additional downgrade due to indirect comparison for PICO 94 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

Key Findings from PICO 31: indirect evidence from 4 observational studies

- Four observational studies were included, one of which only provided data on infectious complications. None of these studies provide direct evidence that specifically addresses whether anti-TNF therapy is beneficial compared to no anti-TNF therapy as a first-line treatment for CTD-ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 31.

Table 94-1. PICO 94: Excluded Studies

Reference	Reason for Exclusion
Dixon et al., 2010[1]	No comparator of interest
Chen et al., 2022[2]	No comparator of interest
Kang et al., 2020[3]	No comparator of interest
Zamora-Legoff et al., 2016[4]	No comparator of interest

References for PICO 94

1. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Annals of the rheumatic diseases*. 2010;69(6):1086-91. doi:https://dx.doi.org/10.1136/ard.2009.120626
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References for Included Studies for PICO 26

1. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *The New England journal of medicine.* 2006;354(25):2655-66.
2. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
3. Jensen ML, Lokke A, Hilberg O, Hyldgaard C, Bendstrup E, Tran D. Clinical characteristics and outcome in patients with antisynthetase syndrome associated interstitial lung disease: a retrospective cohort study. *European clinical respiratory journal*. 2019;6(1):1583516. doi:https://dx.doi.org/10.1080/20018525.2019.1583516
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7. Steen VD, Lanz JK, Jr C, C O, G. R M, T. A, Jr. Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. *Arthritis and rheumatism*. 1994;37(9):1290-6.
8. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
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11. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *American journal of respiratory and critical care medicine*. 2008;177(1):91-8.
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References for Included Studies for PICO 31

1. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004
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5.

PICO 95: In rheumatic disease patients with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 95, we provide indirect evidence from PICO 34 (IL-6 receptor antagonists vs no IL-6 receptor antagonists as first line ILD treatment) and PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Low for PICO 34. An additional downgrade due to indirect comparison for PICO 95 resulted in a rating of Very low (for IL-6 receptor antagonists) and Very low (for cyclophosphamide).

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

Key Findings from PICO 34: indirect evidence from 4 studies (2 RCTs, and 2 observational studies):

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.

- The aforementioned study's preceding phase 2 randomized controlled trial demonstrated slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a post hoc analysis of the aforementioned RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.
- One observational study of SSc patients reported no difference for FVC% predicted with tocilizumab vs without tocilizumab at 12 months.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 34.

Table 95-1. PICO 95: Excluded Studies

Reference	Reason for Exclusion
Suleman et al., 2021[1]	Wrong study design

References for PICO 95

1. Suleman Y, Clark KEN, Cole AR, Ong VH, Denton CP. Real-world experience of tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase-positive patients. *Rheumatology (Oxford, England)*. 2021;60(8):3945-3946. doi:https://dx.doi.org/10.1093/rheumatology/keab273

References for Included Studies for PICO 26

1. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *The New England journal of medicine.* 2006;354(25):2655-66.
2. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
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10. Clements PJ, Roth MD, Elashoff R, et al. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. *Annals of the rheumatic diseases*. 2007;66(12):1641-7.
11. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *American journal of respiratory and critical care medicine*. 2008;177(1):91-8.
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14. Goldin J, Elashoff R, Kim HJ, et al. Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: *findings from the scleroderma lung study*. Chest. 2009;136(5):1333-1340. doi:https://dx.doi.org/10.1378/chest.09-0108
15. Kim HJ, Brown MS, Elashoff R, et al. Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. *European radiology*. 2011;21(12):2455-65. doi:https://dx.doi.org/10.1007/s00330-011-2223-2
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5.

PICO 96: In rheumatic disease patients with ILD, what is the impact of abatacept compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 96, we provide indirect evidence from PICO 32 (abatacept vs no abatacept as first line ILD treatment) and PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Very Low for PICO 32. An additional downgrade due to indirect comparison for PICO 96 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 follow-up studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a non-statistically significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

Key findings from PICO 32: indirect evidence from 3 observational studies

- One retrospective study without a comparator group evaluated 16 RA-ILD patients who received abatacept for at least one year. No patients had a worsening in ILD severity during the study period.
- In one small retrospective study that included 44 patients who received abatacept and 31 patients who received a JAKi, there was no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.
- Although the differences were small, one retrospective study of RA-ILD patients demonstrated that receiving abatacept vs any form of TNFi may be associated with a decreased risk of ILD exacerbation or serious respiratory complications.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 32.

Table 96-1. PICO 96: Excluded Studies

Reference	Reason for Exclusion
Nakashita et al., 2016[1]	Wrong study design
Tardella et al., 2022[2]	No comparator of interest
Kang et al., 2020[3]	No intervention of interest

References for PICO 96

1. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respiratory investigation*. 2016;54(5):376-9. doi:https://dx.doi.org/10.1016/j.resinv.2016.03.001
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PICO 97: In rheumatic disease patients with ILD, what is the impact of JAK inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key findings:

- One retrospective observational study (Fan et al. 2022)[1] found that among patients with MDA5-related interstitial lung disease, treatment with tofacitinib was associated with lower 6-month (p=0.03) and 12-month (p=0.03) mortality when compared to treatment with tacrolimus.
    - This association was maintained at 12 months after adjustment for age, sex, smoking history, MDA5 titer and concurrent medication use (HR 0.44; 95% CI 0.20-0.96; p=0.04).
- A second retrospective observational study (Tardella et al. 2022) [2] found that among patients with RA-ILD with ≥10% extent of fibrosis on HRCT, treatment with a JAK inhibitor (either tofacitinib or baricitinib) was associated with a nominally lower risk of ILD progression on HRCT (16.1% vs 11.3%).
    - ILD progression on HRCT was measured quantitatively.
    - Inference testing was not performed between treatment groups.

Summary: We included two retrospective observational studies that indirectly addressed this PICO. No direct evidence comparing JAK inhibitors to cyclophosphamide was identified. No randomized controlled trials were identified.

Results from RCTs: None performed

Results from non-randomized studies of interventions (NRSI): Two NSRIs provide very low-quality evidence that JAK inhibitors may result in better survival when compared to tacrolimus in patients with MDA5-related ILD and lower the risk of HRCT progression of ILD when compared to abatacept in patients with RA-ILD. Both studies suffer from indication bias, which likely explains the lack of inference testing between treatment groups in Tardella et al. 2022.[2] The proportion of patients in Fan et al. 2022[1] who developed an infection was higher in the tofacitinib group (42.3%) compared to the tacrolimus group (31.4%). Safety was not assessed in the Tardella study.

Table 97-1: JAK inhibitors vs cyclophosphamide as first line ILD treatment

Author, year	Study design	Risk of bias	Time of reassessment	Population Description	Screening or assessment measures	Results
Fan et al. 2022 [1]	Retrospective observational study	High		MDA5-ILD patients treated with either Tofacitinib or TAC	26 patients were treated with TOF and 35 were treated with TAC	Entire group TOF TAC 6-month mortality 10 (38.5%) 22 (62.9%) P=0.03 1-year mortality 11 (44.0%) 23 (65.7%) p=0.03 RP-ILD TOF TAC 6-month mortality 10 (76.9%) 21 (95.5%) p=0.02 1-year mortality 11 (84.6%) 22 (100%) p=0.02
Tardella et al. 2022[2]	Retrospective observational study	High		75 RA-ILD patients who received either JAKis or abatacept. Seventy-five patients (69.3% women) were evaluated, 31 received a JAKi while 44 received ABA.	31 patients who received a JAKi and 44 patients who received Abatacept. Computer-aided method (CaM) used to assess changes in (HRCT) fibrosis percentage and classify patients as worsened (15% more), stable, or improved (15% less) fibrosis after 18 months.	Abatacept JAKis Time 0 Time 18 Time 0 Time 18 DLCO 58.69 61.36 59.72 62.77 FVC 82.29 81.24 81.18 79.59 HRCTcam 19.41 18.94 18.54 17.52 All p values NS CT deterioration Stability Improved ABA 5 (11.4%) 32 (72.6%) 7 (16%) JAKis 5 (16%) 20 (65.5%) 6 (19.4%)

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PICO 98: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very Low**

Due to the lack of direct evidence for PICO 98, we provide indirect evidence from PICO 38 (nintedanib vs no nintedanib as first line ILD treatment) and PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Moderate to Low for PICO 38. An additional downgrade due to indirect comparison for PICO 98 resulted in a rating of Low (for nintedanib) to Very low (for cyclophosphamide).

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.

    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.
    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs ((SENSCIS)(INBUILD)) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS)(INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 26 and PICO 38.

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PICO 99: In rheumatic disease patients with ILD, what is the impact of pirfenidone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- No studies providing direct evidence were identified for this PICO, but several providing indirect evidence for pirfenidone, or cyclophosphamide compared to other immunosuppressants or placebo were included.
- Chen et al 2022[1] conducted an uncontrolled prospective cohort analysis of pirfenidone plus tacrolimus and corticosteroids (n=22) compared to tacrolimus and corticosteroids alone (n=12) and found no difference in the primary endpoint of 12-month cumulative survival between groups. They observed that combination therapy with pirfenidone was associated with lower visual fibrosis scores on chest computed tomography (p=0.021) and a lower rate of respiratory-related relapse rates (p=0.0029).
- Acharya et al 2020[2] conducted a double-blind RCT (n=29) and reported no difference between pirfenidone and placebo in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months of follow-up. Results suggest that a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD.
- Solomon et al 2022 [3] conducted a phase 2 RCT (TRAIL1) comparing pirfenidone to a placebo in patients with RA-ILD, which was stopped early due to slow recruitment. Among 123 randomized patients, no significant difference between pirfenidone vs. placebo in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death). Among secondary endpoints, those treated with pirfenidone had a slower rate of FVC decline over 52-weeks compared to placebo (-66mL vs -146mL; p=0.0082). Hospitalizations and respiratory exacerbations were similar between the groups, and there was no significant difference in all-cause mortality.
- Behr et al 2021 [4] conducted a double-blind, phase 2b RCT (RELIEF) comparing pirfenidone to placebo in patients with diverse forms of non-IPF ILD, including CTD-ILD, which was stopped due to slow recruitment. Among 127 randomized participants, which included 37 patients with progressive CTD-ILD, there was significantly lower 52-week decline in FVC % predicted in the pirfenidone group compared with placebo in the pre-specified rank ANCOVA analysis (p=0.043).
- Tashkin et al., 2006,[5] a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group (p<0.03), but no difference in unadjusted change in FVC%.

- Hoyles et al., 2006,[6] a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant (p=0.08) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.[7,8,9,10,11,12]

Summary: No studies providing direct evidence for this PICO were identified. Studies providing potential indirect evidence for pirfenidone or cyclophosphamide compared to either placebo or in conjunction with immunosuppressants other than cyclophosphamide were included.

First was a small, uncontrolled prospective cohort study by Chen et al 2022.[1] Authors prospectively followed 38 patients treated with tacrolimus plus corticosteroids and compared those treated with tacro/CS (n=12) to those treated with these immunosuppressants plus pirfenidone (n=22). Inverse probability weighting was used in an attempt to account for confounding by indication, but no patients were excluded. Authors found no difference in the primary endpoint of 12-month cumulative survival between groups. They observed that combination therapy with pirfenidone was associated with lower visual fibrosis scores on chest computed tomography (p=0.021) and a lower rate of respiratory-related relapse rates (p=0.0029). Respiratory-related relapse was defined as Respiratory-related relapse was defined as the exacerbation of respiratory-related symptoms combined with radiological progression of ILD evaluated by both rheumatologists and radiologists. A large number of analyses were performed, and p-values were not adjusted for multiple testing. Despite the analytic approach, the risk of selection bias and confounding by indication was high, making findings very low quality. Second, we include a small proof of concept/pilot study, Acharya et al., 2020.[1] This double-blind RCT study examined pirfenidone (n=16) vs. placebo (n=13) in SSc-ILD patients and failed to achieve its primary endpoint with no difference in the proportion of subjects achieving either improvement or stabilization in FVC at 6 months in the pirfenidone vs. placebo groups. It also failed to find a significant beneficial effect of pirfenidone over placebo in improving exercise capacity or respiratory symptoms. This study was underpowered to provide conclusive evidence. However, only one subject (5.9%) had worsening lung functions in the pirfenidone group, compared to 4 (23.5%) subjects in the placebo group, but not statistically significantly different. In subjects with a UIP pattern on HRCT, 5/6 (83.3%) receiving pirfenidone remained stable vs. only 2/5 (40%) subjects in the placebo group remained stable, suggesting a better response with pirfenidone might be observed in subjects with a UIP pattern of ILD. For additional information, please see the Executive Summaries, and data provided in SOF/Word tables under PICO 39.

Next, was a phase 2 RCT (TRAIL1) by Solomon et al., 2022[2], (n=123) in RA-ILD. Patients were randomly assigned (1:1) to receive 2403 mg oral pirfenidone or placebo daily. The trial was stopped early (March 31, 2020) due to slow recruitment and the COVID-19 pandemic. The difference in the proportion of patients who met the composite primary endpoint (decline in FVC% from baseline of 10% or more or death) between the two groups was not significant (seven [11%] of 63 patients in the pirfenidone group vs. nine [15%] of 60 patients in the placebo group; OR 0.67 [95% CI 0.22 to 2.03]; p=0.48). See Table 39-1. Compared with the placebo group, patients in the pirfenidone group had a slower rate of decline in lung function, measured by the estimated annual change in absolute FVC (–66 vs. –146; p=0.0082) and FVC% (–1.02 vs. –3.21; p=0.0028). In addition, 34 (54%) of 63 patients with usual interstitial pneumonia in the pirfenidone group had a significantly smaller reduction in annual change in FVC at 52 weeks compared with 47 (78%) of 60 patients with usual interstitial pneumonia in the placebo group (–43 mL vs. –169 mL; p=0.0014).The groups were similar with regards to the decline in FVC% by 10% or more (five [8%] participants in the pirfenidone group vs. seven [12%] in the placebo group; OR 0.52 [95% CI 0.14–1.90]; p=0.32) and the frequency of progression as defined by OMERACT (16 [25%] in the pirfenidone group vs. 19 [32%] in the placebo group; OR 0.68 [0.30–1.54]; p=0.35). While there were more treatment-emergent AEs in the pirfenidone group and treatment-related AEs leading to drug discontinuation in the pirfenidone arm, these were mild grade 1, and most common were GI side effects (nausea). There was no significant difference in the treatment-emergent serious adverse events rate between the two groups, and there was no difference in treatment-related deaths. For additional information, please see the Executive Summaries, and data provided in SOF/Word tables under PICO 39.

Next was a double-blind, randomized, placebo-controlled, parallel phase 2b trial (RELIEF) by Behr et al[3], which randomly assigned 127 patients (1:1) to either oral pirfenidone (n=64) (267 mg three times per day in week 1, 534 mg three times per day in week 2, and 801 mg three times per day thereafter) or matched placebo (n=63), added to their ongoing medication for progressive fibrotic ILD due to 4 diagnoses: collagen or vascular diseases (i.e., connective tissue disease-associated ILDs), fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis. The study was prematurely terminated at 48 weeks on the basis of an interim analysis for futility triggered by slow recruitment. This caused a failure to achieve the intended power and caused a high number of missing values as patients did not complete the trial as planned. Despite this, a treatment effect was noted in the prespecified primary endpoint analysis. A significantly lower decline in FVC % predicted in the pirfenidone group was noted compared with placebo (p=0·043); the result was similar when the model was stratified by diagnostic group (p=0·042). The study suggested that in patients with fibrotic ILDs other than IPF who deteriorate despite conventional therapy, adding pirfenidone to existing treatment might attenuate disease progression as measured by a decline in FVC. In the analyses of secondary endpoints, no significant difference was found between the pirfenidone and placebo groups with regard to progression-free survival. The safety and

tolerability profile of pirfenidone was similar to that described in previous IPF trials. One death (non-respiratory) occurred in the pirfenidone group (2%) and five deaths (three of which were respiratory) occurred in the placebo group (8%). The most frequent serious adverse events in both groups were infections and infestations (5 [8%] in the pirfenidone group, 10 [16%] in the placebo group); disease worsening (two [3%] in the pirfenidone group, seven [11%] in the placebo group); and cardiac disorders (one ([2%] in the pirfenidone group, 5 [8%] in the placebo group). Adverse events (grade 3–4) of nausea (two patients on pirfenidone, two on placebo), dyspnea (one patient on pirfenidone, one on placebo), and diarrhea (one patient on pirfenidone) were also observed. For additional information, please see the Executive Summaries, and data provided in SOF/Word tables under PICO 39.

When assessing cyclophosphamide compared to placebo or other immunosuppressants, we found indirect evidence to address this PICO from 2 randomized controlled clinical trials of low quality (Tashkin et al., 2006,[5] Hoyles et al., 2006[6]), 6 observational studies(Jensen et al., 2019,[7] Tzelepis et al., 2007, [8] Nakamura et al., 2021,[9] Adler et al., 2018,[10] Steen et al., 1994[11,] Fu et al., 2019[12]) and 8 follow-up studies(Furst et al., 2011,[13] Clements et al., 2007, [14] Strange et al., 2008, [15] Tashkin et al., 2007, [16] Theodore et al., 2012, [17] Goldin et al., 2009, [18] Kim et al., 2011, [19] Kim et al., 2016,[20]) of an RCT (Tashkin et al., 2006[5]).

For RCTs, Tashkin et al., 2006[5] is a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide (CYC) versus placebo in 158 scleroderma ILD patients presented in Table 26-1 and Table 26-2. This study met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$). Table I provides the analyses of unadjusted FVC, DLCO, TLC, SF36, and skin thickness showing statistically non-significant improvements in the CYC group, but a statistically significant improvement in HAQ scores. No statistically significant differences were observed with regard to serious adverse events, pneumonia, anemia, hematuria, and deaths, but the CYC did have a significantly higher rate of leukopenia. Table 26-2 is a summary of 8 studies that performed additional analyses on the original RCT. Important findings from these studies show that the change in FVC seen at 1 year, was not observed after 2 years. [16] Theodore et al., 2012[17] reported similar benefits in patients reporting cough at 1 year, but not 2 years. Clements et al., 2007[14] analyzed the change in FVC in limited and diffuse SSc and observed a significant improvement in patients with limited disease, but not diffuse disease. Furst et al., 2011[13], reported an increase in total adverse events in the CYC group at year 1 ($p=0.002$), primarily driven by an increase in hematologic adverse events ($p=0.001$), in particularly leukopenia ($p<0.0001$). No differences were observed in a number of deaths between groups. Strange et al., 2008[15] reported that more patients with abnormal BAL had a response to CYC compared to placebo. Lastly, 3 studies reported improvements in high-resolution CT fibrosis scores through various methodologies in the CYC group compared to the placebo group.[18-20] Hoyles et al., 2006[6] is a double-blinded, randomized, placebo-controlled clinical trial of 6 months

of cyclophosphamide followed by azathioprine maintenance versus placebo, in 45 scleroderma ILD patients, presented in Table 26-3. This trial demonstrated a statistically non-significant (p=0.08) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group compared to the placebo group at 12 months. For additional information, please see the Executive Summaries, and data provided in SOF/Word tables under PICO 26.

For observational studies, Jensen et al., 2019 [7] reported on 12 patients with anti-synthetase syndrome ILD, with 7 patients treated with CYC and steroids compared to 2 patients treated with steroids alone. The CYC+steroids group had a statistically significant, larger improvement in FVC and DLCO compared to the steroids alone group. Tzelepis et al., 2007[8] reported on 59 patients with SSc-ILD, 29 treated with CYC v 30 not treated with CYC. Patients treated with CYC were more likely to have an improvement in FVC by at least 10% than no CYC (RR 4.14, 0.96-17.87). Adler et al., 2018[10] reported on the EUSTAR SSc cohort and reported no benefit of CYC in patients with DLCO < 50%; no other data were attributable to CYC versus no CYC. Lastly, Steen et al., 1994[11], reported on a cohort of 122 patients with SSc ILD. Individuals treated with CYC but no other immunosuppressants were the only group to show improvements in FVC% from baseline to the end of the study (P<0.05). However, there was an increase in non-pulmonary mortality. Nakamura et al., 2021[9] compared rheumatoid arthritis ILD patients with an acute exacerbation treated with steroids and CYC to propensity-matched RA-ILD acute exacerbations treated with steroids but not CYC. Results indicated no differences in mortality, discharging on oxygen, or duration of mechanical ventilation but showed higher rates of the need for platelet transfusions in patients treated with CYC. Fu et al., 2019 performed a Cox regression analysis of a retrospective cohort of RA-ILD patients and observed an improved survival in RA-ILD treated with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, P < 0.01).[12] For additional information, please see the Executive Summaries, and data provided in SOF/Word tables under PICO 26.

Table 99-1. PICO 99: Excluded Studies

Reference	Reason for Exclusion
Li et al., 2016[5]	No comparator of interest

References for PICO 99

1. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. *Front Immunol*. 2022;13:978429. doi:10.3389/fimmu.2022.978429

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12. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
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PICO 100: In rheumatic disease patients with ILD, what is the impact of IVIG compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 100, we provide indirect evidence from PICO 40 (IVIG vs no IVIG as first line ILD treatment) and PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 26 and Very Low for PICO 40 (no evidence addressing). An additional downgrade due to indirect comparison for PICO 100 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a non-statistically significant ($p=0.08$) trend towards improved FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results about treatment benefit of CYC.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 26.

Table 100-1. PICO 100: Excluded Studies

Reference	Reason for Exclusion
Danieli et al. 2014[1]	Not a comparator of interest
Wang et al. 2022[2]	Not a comparator of interest

References for PICO 100

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References for Included Studies for PICO 26

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18.

PICO 101: In rheumatic disease patients with ILD, what is the impact of oral prednisone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

1 RCT comparing IV cyclophosphamide (CYC) with a combination of CYC plus prednisone (PRED) indirectly addresses this PICO. Results indicated the following:

- After 12 months of treatment, there was no improvement in PFTs (FVC, FEV1, and DLCO) in both groups, and they remained stable at 1 and 3 years.
- CYC was effective in stabilizing lung function in NSIP pattern of lung disease for 3 years after 1-year treatment with CYC. The addition of PRED did not bring further improvement regarding lung fibrosis.
- Therapy was well tolerated, with no patient developing scleroderma renal crisis in the CYC+PRED group.

Summary: 1 small RCT indirectly addresses PICO 101.[1]

This is a prospective, open-label, randomized, controlled trial for the treatment of NSIP in SSc. Eighteen patients with systemic sclerosis and lung biopsy-proven non-specific interstitial pneumonia were randomized sequentially to receive either CYC alone (first 9 patients) or CYC plus PRED for 12 months (last 9 patients). The primary outcome was a change in pulmonary function tests at 12 months and 3 years. Secondary outcomes were modified Rodnan skin score changes at the same time points and mortality (see Table 1). At baseline, both groups were similar in age, disease duration, skin involvement, and anti-topoisomerase positivity but a percentage of limited SSc and current/ex-smokers was higher in the CYC group. At 1 year, the change in FVC, FEV1, and DLCO-Hb were similar in CYC versus CYC+ PRED group. The occurrence of cellular or fibrotic NSIP patterns did not correlate with changes in pFTs. At 3 years follow-up, a trend towards improvement of DLCO-Hb (p=0.08) was seen in CYC- PRED group. The mRSS score improved significantly in the CYC+ PRED group at one year (14.88 ±12.62 at baseline to 9.05 ±9.85, p=0.02) but did not change in the CYC alone group. At 3 years, values remained stable in both groups. Mortality and infection were similar between groups.

Table 101-1: PICO 101: Oral prednisone vs. cyclophosphamide as first-line ILD treatment (indirectly addresses)

Author, Study,	Study	Risk of Bias	Follow-up	Population description	Treatment comparator	Results
Domiciano et al., 2011[1]	Prospective, open-label, sequential randomized, controlled trial in SSc	Low	3 years	24 patients underwent surgical lung Bx, 6 excluded (4 with centrilobular fibrosis as a pattern more common with GERD, 1 with isolated bronchiolitis due to smoking and 1 with isolated PH). N=18, SSC patient with NSIP on surgical lung Bx, randomized sequentially into IV CYC monthly 1 g/m2 X 12 months (first nine patients) and group 2 with CYC similar as group I + prednisone 60 mg X 1 month tapered (? Schedule) to 10 mg /day at the end of the second month and same dose maintained till 12 months. Age 46 y in CYC and 41 y (p=0.23), Limited disease in 33% CYC group and 56% in CYC+PRED group, diffuse d'se in 66% in CYC and 44% in CYC+PRED. Disease duration 6 years in both groups (p=0.45). 44% ex-smokers and 11% current smokers in CYC group and all nine	IV CYC 1 g/m2 monthly (n= 9) vs. IV CYC+ oral prednisone (n= 9)	FVC%: At 1 year, change in FVC% in CYC group was 67.33 ±6.43 to 65.22± 17.54 (p=0.76), in the CYC+Pred group it was 64.77± 7.77 to 64.00 ±9.74 (p=0.40); changes in FEV1 in CYC group 69.22 ± 16.88 to 69.33±17.55 (p=0.88) and in CYC+ prednisone group (n=8) 70.66±5.70 to 68.87±10 (p=0.5), changes in DLCO-Hb (n=5) 56.4±9.15 to 41.80±14.38 (p=0.54) and in CYC+pred (n=6) 64.17± 16.75 to 60.17 ±15.25 (p=0.28). DLCO was tested in 5 patients only in both groups. All these changes were similar between CYC and CYC+ prednisone groups. No difference noted if NSIP pattern was fibrotic or cellular NSIP (p=0.57) After completion of 1 year of therapy, changes in PFTs at 3 years were similar in both groups. Change in FVC% in CYC group was 65.22 ± 17.54 to 62.88 ± 18.95 (p=0.39), in the CYC+ Pred group it was 64.00 ±9.74 to 65.43 ± 8.73 (p=0.61); changes in FEV1 in CYC group 69.33±17.55 to 64.00 ± 19.73 (p=0.78) and in CYC+ prednisone group (n=8) 68.87±10 to 66.57 ± 6.80 (p=0.5), changes in DLCO-Hb 41.80±14.38 to 42.80 ± 15.61(p=0.54) and in CYC+pred 60.17 ±15.25 to 65.33 ± 10.89 (p=0.28). mRSS change at the end of 1 year did not change from 24.5 ± 13.36 to 22.44 ± 12.49 in the CYC group (p=0.72) and showed a trend towards improvement in the

Author, Study,	Study	Risk of Bias	Follow-up	Population description	Treatment comparator	Results
				patients in the CYC group were nonsmokers. Primary endpoint: changes in PFTs after 1 and 3 years between groups. Secondary outcome changes in mRSS and mortality rate.		CYC+pred with 14.88 ±12.62 at baseline to 9.05 ±9.85 (p=0.02). At 3 years, mRSS values were similar to those observed at the end of 12 months in both groups and 22.44 ± 12.49 to 20.13 ± in the CYC group (p=0.68) and in the CYC+pred 9.05 ±9.85 to 10.63 ±9.23 (p=0.11). Adverse events: One patient died in each group in the second year of follow-up unrelated to treatment; in CYC it was due to ischemic cardiac failure and aspiration pneumonia in the CYC+pred group. Mortality was not different, and 5-year Kaplan-Meier survival risk assessment did not show any difference between the groups. Similar rates of infection were noted between groups. Cutaneous infection in two patients (1 in each group), sinusitis (1 in CYC group), urinary infection in 2 patients (CYC+PRED), and bacterial pneumonia in one patient (CYC). Two patients (1 in each group) had lymphopenia treated with the reduction in CYC dose to 800 mg/m2. One patient developed nausea and vomiting during infusion of CYC, but no episodes of hemorrhagic cystitis or malignancy were observed.

Table 101-2. PICO 101: Excluded Studies

Reference	Reason for Exclusion
Perez-Campos et al., 2012[2]	No comparator of interest
Fujisawa et al., 2005[3]	No comparator of interest

Reference	Reason for Exclusion
Li et al., 2019[4]	Not a population of interest
Hozumi et al., 2019[5]	No comparator of interest
Bodolay et al., 2005[6]	Wrong study design
Fujita et al., 2005[7]	No outcomes of interest
Friedman et al., 1996[8]	Wrong study design
Chen et al., 2022[9]	No comparator of interest
Zamora-Legoff et al., 2016[10]	Not a comparator of interest
Adler et al., 2018[11]	No outcomes of interest

References for PICO 101

1. Domiciano DS, Bonfa E, Borges CTL, et al. A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma. *Clinical rheumatology*. 2011;30(2):223-9. doi:https://dx.doi.org/10.1007/s10067-010-1493-4
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6. Bodolay E, Szekanecz Z, Devenyi K, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology (Oxford, England)*. 2005;44(5):656-61.
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8. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Seminars in arthritis and rheumatism*. 1996;26(1):459-67.

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10. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z
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PICO 102: In rheumatic disease patients with ILD, what is the impact of intravenous methylprednisolone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 102, we provide indirect evidence from PICO 26 (cyclophosphamide vs no cyclophosphamide as first line ILD treatment) below. No PICO addressed the effectiveness of intravenous methylprednisone as first-line ILD treatment. The certainty of evidence across all critical outcomes was rated Low for PICO 26. An additional downgrade due to indirect comparison for PICO 102 resulted in a rating of Very low.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group ($p<0.03$), but no difference in unadjusted change in FVC%.
- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant ($p=0.08$) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

For additional information, please see the Executive Summary and data provided in Summary of Findings (SOF)/Word tables under PICO 26.

Table 102-1. PICO 102: Excluded Studies

Reference	Reason for Exclusion
Fujisawa et al., 2005[1]	Wrong study design

References for PICO 102

1. Fujisawa T, Suda T, Nakamura Y, et al. Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. *The Journal of rheumatology*. 2005;32(1):58-64.

References for Included Studies for PICO 26

1. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *The New England journal of medicine.* 2006;354(25):2655-66.
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11. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *American journal of respiratory and critical care medicine*. 2008;177(1):91-8.

12. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *American journal of respiratory and critical care medicine*. 2007;176(10):1026-34.
13. Theodore AC, Tseng C-H, Li N, Elashoff RM, Tashkin DP. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: *findings from the Scleroderma Lung Study*. Chest. 2012;142(3):614-621. doi:https://dx.doi.org/10.1378/chest.11-0801
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PICO 103: In rheumatic disease patients with ILD, what is the impact of plasma exchange compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the limited evidence base for PICO 103, we provide indirect evidence from PICO 41 (plasma exchange compared to no plasma exchange as first line ILD treatment) and PICO 26 (cyclophosphamide compared to no cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICOs 103 and PICO 41 and Low for PICO 26.

Key Findings from PICO 103: indirect evidence from 1 observational study

- Compared to the standard of care with intravenous corticosteroids and various immunosuppressive therapies, the addition of plasma exchange was associated with improved one-year transplant-free survival.

Summary: Bay et al., 2022[1] conducted a single-center retrospective analysis of patients with rapidly-progressive MDA-5 positive myositis-associated ILD that showed the addition of plasma exchange to the standard of care with intravenous corticosteroids and various immunosuppressive therapies (n=25) was associated with increased one-year transplant-free survival when compared to patients who received standard of care alone (n=26). In outcome analysis, 20% of those receiving PLEX met a composite endpoint of death or lung transplant at 12 months compared to 54% of those not receiving PLEX (p=0.01). The study likely suffered from indication bias and was judged to be of low quality.

Key Findings from PICO 41: indirect evidence from 1 observational study

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

Key Findings from PICO 26: direct evidence from 16 studies (2 RCTs, 6 observational studies, and 8 followup studies of 1 RCT (Tashkin 2006):

- Tashkin et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of cyclophosphamide versus placebo in 158 scleroderma ILD patients, met the primary outcome of mean absolute difference in 12-month FVC percent predicted adjusted for baseline FVC between the CYC and placebo group (p<0.03), but no difference in unadjusted change in FVC%.

- Hoyles et al., 2006, a double-blinded, randomized, placebo-controlled clinical trial of 6 months of cyclophosphamide followed by azathioprine maintenance versus placebo in 45 scleroderma ILD patients, demonstrated a statistically non-significant (p=0.08) trend towards a better change in FVC percent predicted adjusted for baseline FVC in the CYC group.
- Six observational studies in patients with anti-synthetase ILD, RA-ILD and SSc-ILD showed conflicting results with regard to treatment benefit of CYC.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 41 and PICO 26.

Table 103-1. PICO 103: Excluded Studies

Reference	Reason for Exclusion
Tsuji et al., 2020[2]	No intervention of interest

References for PICO 103

1. Bay P, e Chambrun MP, Rothstein V, et al. Efficacy of plasma exchange in patients with anti-MDA5 rapidly progressive interstitial lung disease. *Journal of autoimmunity*. 2022;133:102941. doi:https://protect-us.mimecast.com/s/Yx-rCPNY2LiK7mNQhrKs7Q0?domain=dx.doi.org

2. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105

References for Included Studies for PICO 41

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7.

References for Included Studies for PICO 26

1. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *The New England journal of medicine.* 2006;354(25):2655-66.

2. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis and rheumatism*. 2006;54(12):3962-70.
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8. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x
9. Furst DE, Tseng C-H, Clements PJ, et al. Adverse events during the Scleroderma Lung Study. *The American journal of medicine*. 2011;124(5):459-67. doi:https://dx.doi.org/10.1016/j.amjmed.2010.12.009
10. Clements PJ, Roth MD, Elashoff R, et al. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. *Annals of the rheumatic diseases*. 2007;66(12):1641-7.
11. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *American journal of respiratory and critical care medicine*. 2008;177(1):91-8.
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18.

PICO 104: In rheumatic disease patients with ILD, what is the impact of nintedanib compared to IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 104, we provide indirect evidence from PICO 38 (nintedanib compared to no nintedanib as first line ILD treatment) and PICO 34 (IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Moderate to Low for PICO 38 and Low for PICO 34. An additional downgrade due to indirect comparison for PICO 104 resulted in a rating of Very low.

Key Findings from PICO 38: direct evidence from 8 studies (2 RCTs, 1 open label extension and 4 subgroup analyses for SENSCIS and INBUILD including Distler 2019, Flaherty 2019, Flaherty 2022, Allanore 2022, Matteson 2022, Highland 2021, Assassi 2022, and Hoffman-Vold 2022)

- One RCT (SENSCIS) comprised of 576 patients with Systemic sclerosis (SSc)-associated ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.035$) that favored nintedanib 150 mg twice daily over placebo.
    - All patients enrolled in this study had been diagnosed with SSc-associated ILD.
    - 48.4% of patients were on mycophenolate mofetil (MMF) at baseline. The proportions of patients using MMF at baseline were similar between the nintedanib and placebo arms. However, randomization was not performed according to "baseline mycophenolate use." There were differences in race representation and study region between groups at the baseline.
- A subgroup analysis (Matteson et al., 2022) of another RCT (Flaherty et al., 2019) and (INBUILD) that focused exclusively on the subgroup of 170 patients with autoimmune ILD identified a statistically significant improvement in the rate of decline in the forced vital capacity over 52 weeks ($p = 0.011$) that favored nintedanib 150 mg twice daily over placebo.
    - Subjects enrolled in this RCT exhibited ILD progression within the preceding 24 months despite management deemed appropriate in clinical practice.
    - Use of several concomitant therapies (including MMF) at baseline was prohibitive of enrollment.
    - Most subjects (n=127; 74.7%) exhibited the usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT.

    - RA-ILD (n=89; 52.4%) comprised most subjects with autoimmune ILD, followed by SSc-ILD (n=39; 22.9%).
- In both RCTs ((SENSCIS)(INBUILD)) and their associated secondary analyses, there were no statistically significant differences in mortality between the nintedanib and placebo groups.
- In both RCTs (SENSCIS)(INBUILD) and their associated secondary analyses, there were no statistically significant differences in self-reported health-related quality of life (HRQOL) between the nintedanib and placebo groups.
- The types of most frequent adverse events were similar across patients with autoimmune ILD in both RCTs. Diarrhea was the most frequent adverse event in both studies. The use of nintedanib was associated with a higher risk of treatment discontinuation ($p < 0.01$). Diarrhea was the most frequent adverse event leading to treatment discontinuation.
-

Key Findings from PICO 34: indirect evidence from 3 studies (2 RCTs and 1 post hoc analysis (Roofeh et al. 2021):

- One phase 3 randomized controlled trial demonstrated a slower decline in FVC % predicted in a large cohort of SSc patients with and without already established ILD. In addition, this study looked across multiple different quality-of-life scoring metrics to include more patient-centered secondary outcomes. Although this study provides important evidence to suggest tocilizumab may be a beneficial first-line treatment of SSc-ILD, its major limitation is the study's inclusion of non-ILD patients in addition to SSc patients with already established ILD.
- The aforementioned study's preceding phase 2 randomized controlled trial demonstrated slower decline in FVC % predicted at 24 and 48 weeks from baseline among patients receiving tocilizumab versus placebo. There was also a significantly smaller decrease in absolute FVC (mL) at 24 weeks in patients who received tocilizumab, although this difference did not persist out to 48 weeks.
- However, a post hoc analysis of the aforementioned RCT looked at the benefits of tocilizumab, specifically in patients with already established but less advanced ILD, and showed similar efficacy as it relates to slower FVC decline and radiographic progression.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 38 and PICO 34.

References for Included Studies for PICO 38

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *The New England journal of medicine*. 2019;380(26):2518-2528. doi:https://dx.doi.org/10.1056/NEJMoa1903076

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4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020
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PICO 105: In rheumatic disease patients with ILD, what is the impact of referral for stem cell transplant compared to optimal medical management as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- One randomized, open-label, phase 2 clinical trial (SCOT), reported improved event-free and overall survival with myeloablative autologous hematopoietic stem cell transplant vs cyclophosphamide (CYC) in patients with severe scleroderma and renal or pulmonary involvement (active ILD). Transplants were associated with increased toxicity.
- One randomized, open-label, phase 3 clinical trial (ASTIS) reported improved long-term event-free survival, better overall survival and lung function with autologous hematopoietic stem cell transplant (HSCT) vs CYC in patients with diffuse cutaneous systemic sclerosis. HSCT was associated with early treatment-related deaths and more Grade 3 or 4 adverse events.

Summary:

The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial,[1] examined 75 patients with severe scleroderma and renal or pulmonary involvement (active ILD) and disease duration <5 years. 36 individuals were randomly allocated to myeloablative, autologous stem cell transplantation while 39 individuals were allocated to CYC. In the intent-to-treat population, transplant was favored over CYC for the global rank composite score at 54 months (1404 (36x39) pairwise comparisons: 67% vs 33%, p=0.01) and 48 months (68% vs 31%, p=0.008). Results for event-free survival and overall survival also favored transplant over CYC. At 72 months, treatment-related mortality was higher with transplant (6% vs 0%), as were serious adverse events (74% vs 51%), and the rate of infection per person-year (2 events vs 1.2 events). Lastly, Zoster occurred in 36% of Tx patients.

The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial,[2] a multicenter randomized open-label, parallel-group clinical trial, assessed the efficacy of autologous hematopoietic stem cell transplant (HSCT) vs CYC in individuals with diffuse systemic sclerosis with maximum disease duration of 4 years. 79 individuals were allocated to HSCT, while 77 individuals were treated with CYC. Benefits to autologous HSCT over CYC included better long-term event-free survival, overall survival, and lung function. Time-varying hazard ratios (HRs) for the primary outcome of death or major organ failure was 0.52 (95% CI: 0.28 to 0.96, p=0.04) at 1 year, and 0.35 (95% CI: 0.16 to 0.74, p=0.006) at 4 years. Time-varying HRs for mortality were 0.48 (95% CI: 0.25 to

0.91, p=0.002) at 1 year and 0.29 (95% CI: .13 to 0.64, p=0.002) at 4 years. Mean change in FVC % predicted was -9.1% (95% CI: -14.7 to -2.5, p=0.004), while no difference was reported in DLCO % predicted. HSCT was associated with early treatment-related deaths (8 vs 0), and more Grade 3 or 4 adverse events rates (63% vs 37%).

PICO 105-1: stem cell transplant vs optimal medical management as first line ILD treatment

Author, Study	Study	Risk of Bias	Follow-up	Population description	Treatment comparator	Results
Sullivan et al. 2018[1] SCOT trial	Randomized, open-label, phase 2, clinical trial, SCOT trial (Scleroderma: Cyclophosphamide or Transplantation)	High	54 months	1. Patients with severe scleroderma with renal or pulmonary involvement (active ILD) and disease duration < 5 years assigned to myeloablative, autologous stem cell transplantation (Tx) (n=36; mobilized 34 and Tx in 33) or CYC (n=39). 27 patients completed trial, 3 died and 6 withdrew prematurely. 2. Exclusion gastric antral vascular ectasia, DLCO < 40% predicted, FVC < 45% predicted, LVEF < 50%, CrCl< 40 ml/min, PAH or > 6 months of treatment with CYC. 2. Primary endpoint – Global rank composite score	1. IV cyclophosphamide (CYC) 500 mg/m2 followed by 11 monthly infusions at 750 mg/m2 (n=39,37 initiated Rx, 32 received 12 doses and 34 received 9 or more doses. 19 patients completed trial, 9 withdrew prematurely and 11 died. 2. Lung involvement seen in 95% in CYC group. Mean FVC 73.8 ± 17 % predicted, mean DLCO 52.7± 8.2	Global rank compositive score (GRCS) (primary efficacy end point): ITT population at 54 months, transplantation favored over CYC (67% of 1404 pairwise comparisons favored Tx vs 33% favored CYC, p=0.01). At 48 months, transplantation was also favored over CYC (68% vs 32%, p=0.008). Event-free survival (survival without respiratory, renal, or cardiac failure) in the per-protocol population (individuals who received a transplant or completed ≥9 doses of CYC) at 54 months was 79% in the Tx group and 50% in the CYC group (p=0.02). At 72 months, the rate of event-free survival was 74% in Tx group and 47% in the CYC group (p=0.03). Overall survival: rate of 86% with Tx vs. 51% with CYC (p=0.02). Rates in ITT population were consistent with these results. Disease modifying agents were introduced at 54 months in 9% of Tx versus 44% in CYC (p=0.001).

				comparing participants on a hierarchy of disease features namely death, survival without renal, cardiac or respiratory failure, forced vital capacity (FVC), HAQ-DI, and mRSS. Secondary endpoint individual components of the global rank composite scores, measures of disease progression and quality of life. Safety endpoints were treatment related death, death from any cause, treatment related toxic effects, infections and hematologic engraftment. Death, cancers, and disease -progression events that occurred after an event were tracked. 3. Protocol was myeloablation with TBI (800cGy), Cyclophosphamide 120 mg/kg and equine ATG 90 mg/kg. After conditioning,		<u>Treatment related mortality</u> in transplantation group was 3% at 54 months and 6% at 72 months compared to 0% in CYC group. <u>Serious adverse events (SAEs)</u>: At 72 months, participants with serious adverse events were lower in CYC vs transplant (51% vs 74%). Based on duration of follow-up, the rate of adverse events was 0.38 with transplantation and 0.52 with CYC (p=0.08). In the Tx group, 96% of SAEs occurred in the first 26 month vs 71% of SAEs in CYC. Patients with grade 3 or higher adverse events were more common in in the transplant group: 2 events per person-year vs. 1.2 events per p-y in CYC (p<0.001). Cancers occurred in 4 participants in Tx versus 1 in CYC. Serious infections were similar (0.75 in Tx and 0.79 in CYC). Rate of infection of grade 3 or higher was more with Tx (0.21 vs 0.13 p=0.09) with most events occurring in 26 months. Lastly, Zoster occurred in 36% of Tx patients.

				followed by reconstitution with a CD34+ cells (median 5.6 X 106 cells/kg 4. Lung involvement seen in 100% of Tx group. Mean FVC 74.5 ± 14.8 % predicted, mean DLCO 53.9± 7.6		
van Laar et al. 2014[2] ASTIS trial	Multicenter, randomized open label, parallel group clinical trial, Autologous Stem cell transplantation international scleroderma (ASTIS trial) to assess efficacy of autologous hematopoietic stem cell transplant (HSCT) versus cyclophosphamide in diffuse systemic sclerosis with maximum disease duration of 4 years	High	Median 5.8 years	1. Block randomization in groups of 2,4,6 to either HSCT or CYC. Treatment was allocated within blocks to balance investigational and standard treatment for age ≤ 40 years or > 40 years and disease duration of < 2 years or > 2 years. 2. HSC (harvesting> conditioning regimen IV CYC 200 mg/kg X 4 days and IV rabbit ATG X 3 days, + IV MP X 3 days followed by infusion of CD34+ cells) (n=79). 71 completed treatments. 3. Primary endpoint was event free survival defined as time in days from	IV Cyclophosphamide (n=77) 750 mg/m2 monthly X 12 months. 57 completed treatments	1. 79 patients were randomized to HSCT and 77 to CYC. 75 patients in each group started treatment, 6 patients did not receive allocated Rx. 71 (90%) completed treatment in HSCT and 57 (74%) in CYC group. 2. **Primary endpoint**: Time varying hazard ratios (HR) of primary outcome of death or major organ failure was 0.52 (95% CI 0.28-0.96, p=0.04) at 1 year, 0.35 (95% CI 0.16-0.74, p=0.006 at 2 years and 0.34 (95% CI 0.16-0.74, p=0.006) at 4 years follow up. Time varying HR for mortality were 0.48 (95% CI 0.25-0.91, p=0.02) at 1 year, 0.29 (95% CI, 0.13-0.65, p=0.002) at 2 years, and 0.29 (95% CI 0.13-0.64, p=0.002) at 4 years follow up. 3. Secondary endpoint: Mean change in FVC in HSCT vs control was -9.1 % predicted (95% CI -14.7, -2.5, p=0.004), TLC difference -6.4% (95% CI -11.9 vs. -0.9, p=0.02). No significant difference was reported in DLCO % predicted. <u>Death</u> 8 control patients received rescue HSCY after 2 years and 1 died

				randomization until occurrence of death from any cause or development of organ failure (heart, renal and lung). Secondary end points were treatment related mortality, toxicity, and changes in mRSS, organ function, HAQ-DI, body weight, SF-36 and EQ 5-D within 24 months following randomization. The need for IS therapy beyond 12- 24 months was an additional end point. 3. Hazard ratio for event free and OS were time dependent. HSCT patients experienced more events in the first year but had better long-term outcomes.		of treatment complication; 2 patients in HSCT received CYC after 2 years. 4. Smaller number in HSCT versus controls received immunosuppressive therapy between 12-24 months: 15 vs. 28 p=0.02 5. 8 deaths in HSCT related to treatment vs none in control. 7/8 patients were current or former smokers. Grade 3 or 4 adverse events were seen in 63% HSCT vs 37% controls, p=0.002.

Table 105-2. PICO 105: Excluded Studies

Reference	Reason for Exclusion
Launay et al., 2009[3]	No intervention of interest
Wada et al., 2020[4]	Wrong study design
Ciaffi et al., 2022[5]	Duplicate of Ciaffi et al. 2020[6]

References

1. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. *N Engl J Med*. 2018:35–47.

2. Jacob M. van Laar MD, Dominique Farge MD, Jacob K. Sont P, et al. Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial. *JAMA*. 2014;311:2490-2498.

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PICO 106: In rheumatic disease patients with ILD, what is the impact of referral for lung transplant compared to optimal medical management as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- One observational study reported a 1-year unadjusted mortality rate of 17.8 per 100 person years for adults with ILD who underwent lung transplantation and found a 48% relative increase in 1-year mortality rate in adults with SSc undergoing lung transplantation vs adults with non-SSc-related ILD.

Summary: The literature searches identified one low-quality study that indirectly addressed this PICO question. Results indicated a 1-year unadjusted mortality rate among adults with ILD who underwent lung transplantation was 17.8 per 100 person-years. A 48% relative increase in 1-year mortality rate was reported in adults with SSc undergoing lung transplantation vs adults with non–SSc-related ILD (hazard ratio 1.48 [95% confidence interval 1.01–2.17]).

Table 106-1. PICO 106: lung transplant vs optimal medical management as first line ILD treatment

Author, year	Study type	Risk of Bias	Population Description	Treatments	Results
Bernstein et al., 2015[1]	Retrospective cohort study	High	A total of 3,763 adults underwent lung transplantation (3,333 adult patients with ILD, 229 adults with SSc, 201 with PAH)	Lung transplantation	1-year mortality rate in patients with SSc undergoing lung transplantation compared to those with non–SSc-related ILD: hazard ratio 1.48 [95% confidence interval 1.01–2.17]. 1-year unadjusted mortality rate among adults with ILD was 17.8 per 100 person-years.

106-2. PICO 106: Excluded Studies

References	Reasons for exclusion
Chen et al. 2022[2]	No intervention of interest

References

1. Bernstein EJ, Peterson ER, Sell JL, et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. *Arthritis & rheumatology (Hoboken, NJ)*. 2015;67(5):1314-22. doi:https://dx.doi.org/10.1002/art.39021

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PICO 107: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding the combination of nintedanib and mycophenolate compared to adding mycophenolate alone on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings: A subgroup analysis of 279 individuals taking mycophenolate in the SENSCIS trial (nintedanib vs. placebo) indirectly addresses PICO 107. At 52 weeks follow-up, no significant difference was reported in the annual rate of decline in FVC (difference 26.3, 95% CI: -27.9 to 80.6) or change in SGRQ total score (1.6, 95% CI: -1.86 to 5.06). The rate of composite adverse event outcome did not differ between the groups.

Summary: 1 RCT Highland et al., 2021[1] addressed this PICO.

We include evidence from a subgroup analysis of 1 large-high-quality double-blind RCT (Highland et al., 2021, using data from the SENSCIS Trial)[1] in which 576 SSc-ILD patients were enrolled, randomly assigned to, and treated with nintedanib (n=288) or placebo (n=288). A prespecified primary endpoint analysis assessed outcomes by mycophenolate use at baseline. Note, patients were not randomized to MMF but had a personal history of MMF.

139 (48%) of 288 in the nintedanib group and 140 (49%) of 288 in the placebo group were taking mycophenolate at baseline. In patients taking mycophenolate at baseline, the adjusted mean annual rate of decline in FVC was -40.2 mL per year (SE 19.8) with nintedanib and -66.5 mL per year (SE 19.3) with placebo (difference: 26.3 mL per year [95% CI -27.9 to 80.6]) at 52 weeks (see Table 107-1). No heterogeneity was found in the effect of nintedanib versus placebo on the annual rate of decline in FVC between the subgroups by mycophenolate use (p-value for interaction = 0.45). In patients taking mycophenolate at baseline, the adjusted absolute change from baseline in SGRQ total score at week 52 was 0.7 (SE 1.3) with nintedanib and -0.9 (SE 1.2) with placebo (difference: 1.6 [95% CI -1.86 to 5.06]).

The adverse event profile of nintedanib was similar between the 2 groups. Diarrhea, the most common adverse event, was reported in 106 (76%) of 139 patients in the nintedanib group and 48 (34%) of 140 in the placebo group among those taking mycophenolate at baseline.

Overall, nintedanib, in combination with mycophenolate, provided greater numerical preservation of lung function than MMF alone. The combination of mycophenolate and nintedanib offers a safe treatment option for patients with SSc-ILD. More data are needed on the benefits of initial combination therapy versus a sequential approach to the treatment of SSc-ILD, which were not assessed by this study.

Additional Considerations

Allanore et al., 2022[2]: Indirect evidence is noted from the SENSCIS-ON study, an open-label extension of SENSCIS and another drug-drug interaction study (DDI). 444 patients entered the study (197 continued nintedanib from SENSCIS and 247 patients initiated or previously had received a placebo in SENSCIS or DDI study). 52.3% were taking mycophenolate at baseline but were not randomized to receive this drug. FVC decline at 52 weeks in those on MMF and nintedanib versus nintedanib alone was -47.3 ml vs. -71.1 ml; in those initiating nintedanib and on baseline MMF was -22.1 ml compared to -70.1 ml in those initiated on nintedanib alone. There was no direct subgroup comparison of MMF + nintedanib vs. nintedanib but the decline in FVC over 52 weeks was lower in those on concomitant MMF with nintedanib. The safety profile of nintedanib over 52 weeks was similar to that noted in the original SENSCIS trial. Cough was more frequent in those who continued (15.2% vs. 8.7%) or initiated (11.8% vs. 5%) nintedanib while on MMF versus nintedanib alone, respectively. Liver test abnormalities were less frequent in patients on MMF both among those who continued (3.8% vs. 19.6%) and initiated nintedanib (13.5% vs. 25.8%).

Table 107-1: PICO 107: Nintedanib + MMF vs. placebo (MMF at baseline) in SSc-ILD (indirectly addresses)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nintedanib + MMF	No Nintedanib + MMF	Relative (95% CI)	Absolute (95% CI)		
Adjusted annual rate of decline in FVC over 52 weeks, mL per year												
Highland et al., 2021	randomised trials	not serious	not serious	serious[b]	serious[a]	none	139	140	-	MD 26.3 higher (27.9 lower to 80.6 higher)	⨁⨁◯◯ Low	Important
Adjusted absolute change from baseline in SGRQ total score at week 52												
Highland et al., 2021[1]	randomised trials	not serious	not serious	serious[c]	serious[a]	none	139	140	-	MD 1.60 higher (1.86 lower to 5.06 higher)	⨁⨁◯◯ Low	Critical
Adverse events, Any												

Highland et al., 2021[1]	randomised trials	not serious	not serious	serious[c]	serious[a]	none	136/139 (97.8%)	135/140 (96.4%)	**RR 1.01 (0.97 to 1.06)**	**10 more per 1,000 (from 29 fewer to 58 more)**	⊕⊕◯◯ Low	Critical

Adverse events, Serious

Highland et al., 2021[1]	randomised trials	not serious	not serious	serious[c]	very serious[a]	none	36/139 (25.9%)	22/140 (15.7%)	**RR 1.65 (1.02 to 2.65)**	**102 more per 1,000 (from 3 more to 259 more)**	⊕◯◯◯ Very low	Critical

Adverse Events Leading to Treatment Discontinuation

Highland et al., 2021[1]	randomised trials	not serious	not serious	serious[c]	very serious[a]	none	15/139 (10.8%)	9/140 (6.4%)	**RR 1.68 (0.76 to 3.71)**	**44 more per 1,000 (from 15 fewer to 174 more)**	⊕◯◯◯ Very low	Critical

CI: confidence interval; **RR:** risk ratio; **SMD:** standardized mean difference

Explanations

- **a.** <200 patients per arm and/or large absolute risk interval
- **b.** Surrogate outcome for mortality

Table 107-1. PICO 107: Excluded Studies

Reference	Reason for exclusion
Kuwana et al., 2021a[3]	No comparator of interest (no subgroup analysis with those with a history of MMF at the baseline)
Kuwana et al., 2021b[4]	No comparator of interest (no subgroup analysis with those with a history of MMF at the baseline)
Hoffman-Vold et al, 2022[5]	No comparator of interest. This is a post-hoc analysis of pooled data from four trials.
Distler et al, 2019[6]	No comparator of interest. (No subgroup analysis in those on MMF)

References

1. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1

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PICO 108: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding the combination of pirfenidone and mycophenolate compared to adding mycophenolate alone on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 109: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 110: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 111: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding azathioprine compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from two retrospective studies suggests that there is no difference between adding azathioprine compared to adding mycophenolate on disease-related outcomes (i.e., FVC%, DLCO%, at 6- and 12-months of follow-up).
- Evidence from two retrospective studies suggests a similar rate of adverse events among patients treated with azathioprine and those treated with mycophenolate; however, the number of events was very small.
    - Evidence from one study[1] indicated a 3-fold higher rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with mycophenolate (12 [13.0%] vs. 3 [3.9%] at 12 months of follow-up, respectively).

Summary:

We included two very low-quality studies that compared physiologic and drug adverse events (i.e., toxicity) among 46 patients with Polymyositis/Dermatomyositis (PM/DM-ILD)[2] and 212 patients with RA-ILD.[1] The study found no statistically significant difference in FVC % predicted at 6 and 12 months, DLCO % predicted at 6 and 12 months, and medication toxicity between those given azathioprine compared to those given mycophenolate mofetil (see Table 111-1). But the other study shows that FVC% and DLCO% predicted were both higher in patients taking MMF and that adverse events are higher in patients taking AZA.

Table 111-1. PICO 111: Add Azathioprine Compared to Adding Mycophenolate after 1st ILD Therapy

Author, year	Study design	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Mira-Avenado et al., 2013[2]	Retrospective	High due to immortal time bias	6 and 12 months	**Number of patients**: 46 **Age**: 50–56 years **Gender**: men (20) women (26) **Diagnosis:** Polymyositis (PM)/ dermatomyositis (DM) associated ILD who required steroid sparing agent after high	CYC (n=24, average dose 129 mg daily), AZA (n=13, avg dose 130 mg daily) or MMF (n=9, avg dose 2.2 g daily) after steroids; treatment selected at discretion of treating MD	**FVC% (median, IQR)** ***6 months*** AZA 59 (53 to 80) MMF 67 (57 to 90) ***12 months*** AZA 61 (52 to 85) MMF 64 (52 to 81) **DLCO% (median, IQR)**

Author, year	Study design	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
				dose GC due to persistent lung disease or significant symptoms and abnormal PFT; required to have longitudinal follow-up for at least 6 months **Associated disease:** PM: 74%; DM: 26%	***Note***: 13 patients switched therapy at 6 months (toxicity 2, potential toxicity 6, inadequate response 5) - 10 on CYC (4 to AZA, 6 to MMF), 2 on AZA (2 to CYC), 1 on MMF (1 to AZA); unclear how these were analyzed.	***6 months*** (median, IQR) AZA 54 (44 to 65) MMF 64 (58 to 69) ***12 months*** (median IQR) AZA 61 (38 to 74) MMF 63 (50 to 64) **Toxicity** AZA 3 (23%) MMF 4 (44%)
Matson et al., 2022[1]	Retrospective cohort study	High	Median follow-up period of 33months	212 patients diagnosed with RA-ILD	Azathioprine Mycophenolate	**FVC % predicted at 12 months**: Azathioprine 3.34%; Mycophenolate 4.55% **DLCO % predicted at 12 months**: Azathioprine 1.93%; Mycophenolate 3.67% **Adverse events (AEs):** All AE: Azathioprine 18 (19.6%); Mycophenolate 12 (15.6%) GI: Azathioprine 3 (3.3%); Mycophenolate 5 (6.5%) Elevated liver enzymes: Azathioprine 3 (3.3%); Mycophenolate 0 %

Author, year	Study design	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
						Cytopenia: Azathioprine 3 (3.3%); Mycophenolate 2 (2.6%) Recurrent infections: Azathioprine 4 (4.3%); Mycophenolate 2 (2.6%) Non-specific symptoms: Azathioprine 5 (5.4%); Mycophenolate 3 (3.9%) Treatment stopped due to adverse event: Azathioprine 12 (13.0%); Mycophenolate 3 (3.9%)

AZA: azathioprine; CYC: cyclophosphamide; DLCO: diffusing capacity for carbon monoxide; DM: dermatomyositis; FVC: forced vital capacity; MMF: mycophenolate mofetil; PM: polymyositis; ROB: risk of bias

References

1. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

2. Mira-Avendano IC, Parambil JG, Yadav R, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respiratory medicine*. 2013;107(6):890-6. doi:https://dx.doi.org/10.1016/j.rmed.2013.02.015

PICO 112: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective cohort study suggests that there is no difference between adding cyclophosphamide compared to adding mycophenolate on disease-related outcomes.
- Study suggested no difference between adding cyclophosphamide compared to adding mycophenolate and the rate of treatment-related adverse events.

Summary:

We included one very low-quality study that compared physiologic and drug adverse events among 46 patients with Polymyositis/Dermatomyositis (PM/DM-ILD).[1] The study suggested no difference in FVC % predicted at 6 or 12 months, DLCO % predicted at 6 or 12 months, and medication toxicity between those given cyclophosphamide compared to those given mycophenolate mofetil (see Table 112-1).

Table 112-1. PICO 112: Add Cyclophosphamide Compared to Adding Mycophenolate after 1st ILD therapy

Author, year	Study design	Risk of bias (ROB)	Follow-up	Population Description	Treatment: Comparator:	Results
Mira-Avenado, et al., 2013[1]	Retrospective	High due to immortal time bias	6 and 12 months	**Number of patients**: 46 **Age**: 50-56 years **Gender**: men (20) women (26) **Diagnosis:** Polymyositis (PM)/ dermatomyositis (DM) associated ILD who required steroid sparing agent after high dose GC due to persistent lung disease or significant symptoms and abnormal PFT; required to have longitudinal follow-up for at least 6 months	CYC (n=24, avg dose 129 mg daily), AZA (n=13, avg dose 130 mg daily) or MMF (n=9, avg dose 2.2 g daily) after steroids; treatment selected at discretion of treating MD Note: 13 patients switched therapy at 6 months (toxicity 2, potential toxicity 6, inadequate response 5) - 10 on CYC (4 to AZA, 6 to MMF), 2 on AZA (2 to CYC), 1 on MMF (1 to	**FVC% (median, IQR)** ***6 months*** CYC 66 (55 to 87) MMF 67 (57 to 90) ***12 months*** CYC 67 (51 to 79) MMF 64 (52 to 81) **DLCO% (median, IQR)** ***6 months*** CYC 50 (40 to 64) MMF 64 (58 to 69) ***12 months*** CYC 46 (39 to 61) MMF 63 (50 to 64)

Author, year	Study design	Risk of bias (ROB)	Follow-up	Population Description	Treatment: Comparator:	Results
				Associated disease: PM: 74%; DM: 26%	AZA); unclear how these were analyzed	**Toxicity** CYC 12 (50%) MMF 4 (44%)

AZA: azathioprine; CYC: cyclophosphamide; DLCO: diffusing capacity for carbon monoxide; DM: dermatomyositis; FVC: forced vital capacity; MMF: mycophenolate mofetil; PM: polymyositis; ROB: risk of bias.

Table 112-2. PICO 112: Excluded Studies

Reference	Reason for exclusion
Li et al., 2022[2]	No comparator of interest
Tomiyama et al., 2016[3]	No comparator of interest
Goldin et al., 2008[4]	No comparator of interest

References

1. Mira-Avendano IC, Parambil JG, Yadav R, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respiratory medicine*. 2013;107(6):890-6. doi:https://dx.doi.org/10.1016/j.rmed.2013.02.015
2. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases complicated with dermatomyositis: A retrospective analysis. *Medicine*. 2022;101(24):e29108. doi:https://dx.doi.org/10.1097/MD.0000000000029108
3. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku Journal of Experimental Medicine*. 2016;239(4):279-305. doi:https://dx.doi.org/10.1620/tjem.239.297
4. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367. doi:https://dx.doi.org/10.1378/chest.07-2444

PICO 113: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 113-1. PICO 113: Excluded Studies

Reference	Reason for exclusion
Bejan-Angoulvant et al. 2020[1]	Wrong publication type

References

1. Bejan-Angoulvant T, Naccache JM, Caille A, et al. Evaluation of efficacy and safety of rituximab in combination with mycophenolate mofetil in patients with nonspecific interstitial pneumonia non-responding to a first-line immunosuppressive treatment (EVER-ILD): A double-blind placebo-controlled randomized trial. *Respiratory medicine and research*. 2020;78:100770. doi:https://dx.doi.org/10.1016/j.resmer.2020.100770

PICO 114: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 115: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 116: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective cohort study suggests that there is no difference between adding rituximab and mycophenolate compared to mycophenolate alone on disease-related outcomes except for a relative decrease in average prednisone dose in those given rituximab (RTX) with or without mycophenolate (MMF) vs. MMF alone. The rate of adverse events in the control group was not reported.

Summary:

We included one very low-quality study that compared mortality, lung function, CT imaging, prednisone dose, and drug adverse events among 83 patients with connective tissue disease–associated interstitial lung disease (CTD-ILD).[1] The intervention group included those given rituximab RTX with or without MMF, and they were compared to those only given MMF. The study suggested no difference in pre- and post-treatment FVC % predicted, DLCO % predicted, or CT score (Table 116-1). The authors did note a relative decrease in average prednisone dose in those individuals who were given RTX with or without MMF vs. MMF alone. While mortality was reported, the statistical significance of the difference between the two groups was not assessed—the death rate was 3/15 (20.0%) in the RTX and 7/68 (10.3%) in the control groups at 1 year of follow-up. While treatment-related adverse events were reported for the RTX +/- MMF group, the risk of these events in the control group was not reported. Thus, the comparative safety profile of these mediations remains unknown.

Table 116-1. PICO 116: Add anti-CD20 compared to adding MMF after 1st line therapy

Author, year	Study design	Risk of bias (ROB)	Follow-up	Population Description	Treatment: Comparator:	Results
Zhu et al., 2021[1]	Retrospective	High risk of bias (1) differences between intervention and control groups (median ILD duration, baseline DLCO, and underlying type of CTD, and follow-up time) – some correction with propensity score; (2) immortal time bias; (3), not a fair comparison-essentially RTX rescue therapy (with or without MMF) vs. initial treatment with MMF	Post-Tx FVC Post-Tx DLCO Post-Tx CT score Change in average prednisone use 1 year for adverse events	**Number of patients:** 83 **Diagnosis:** CTD-ILD **Age:** 57–61 **% female:** 47-71 **Note:** PFT pre- and post-treatment required; NO comment of requiring progressive ILD (but statistical differences in RTX vs. non-RTX group re: ILD disease duration)	Intervention: RTX +/- MMF (n=15) Control: MMF alone (n=68)	**Mortality** (any follow-up after treatment) RTX 3/15 (20.0%) Control 7/68 (10.3%) ***Not tested for stat. diff.*** **Change in FVC (% predicted, post-Tx—baseline), median (IQR)** RTX -3.0 (-11 to 21) Control 2.0 (-14 to 25) ***No difference after adjusting for confounders*** **Change in DLCO (% predicted, post-Tx—baseline), median (IQR)** RTX -3.0 (-10 to 12) Control 4.5 (-30 to 36) ***No difference after adjusting for confounders*** **Change in CT score (post-Tx—baseline), median (IQR)** RTX 0 (-9 to 1), n=9 Control 0 (-5 to 7), n=19s ***No difference*** **Change in average prednisone dose (post-Tx—baseline), median (IQR)** RTX -0.5 (-2.0 to 1.0), n=14 Control 0 (-2.0 to 1.0), n=65 ***Greater decrease of prednisone dose score in the RTX vs. control (p=0.017)*** **Adverse Events** **Infection at 1 year of follow-up**: RTX: 4 (27%) **Hospitalizations at 1 year of follow-up**: RTX: 1 (7%) **Hypogammaglobulinemia (likely unrelated to treatment)**: RTX: 1 (7%) **Infusion reaction at 1 year of follow-up: RTX**: 1 (7%)

FVC: Forced vital capacity; **IQR**: interquartile range; **MMF**: Mycophenolate; **PFT:** pulmonary function test; **RTX**: rituximab; **Tx**:treatment

Table 116-2. PICO 116: Excluded Studies

Reference	Reason for exclusion
Bejan-Angoulvant et al., 2020[2]	No outcomes of interest
Tomiyama et al., 2016[3]	No comparator of interest
Daoussis et al., 2017[4]	No comparator of interest
Narvaez et al., 2020[5]	No comparator of interest
Bauhammaer et al., 2016[6]	No outcomes of interest
Fui et al., 2020[7]	No comparator of interest
Ebata et al., 2019[8]	No comparator of interest

References

1. Zhu L, Chung MP, Gagne L, et al. Rituximab Versus Mycophenolate in the Treatment of Recalcitrant Connective Tissue Disease-Associated Interstitial Lung Disease. *ACR open rheumatology*. 2021;3(1):3-7. doi:https://dx.doi.org/10.1002/acr2.11210
2. Bejan-Angoulvant T, Naccache JM, Caille A, et al. Evaluation of efficacy and safety of rituximab in combination with mycophenolate mofetil in patients with nonspecific interstitial pneumonia non-responding to a first-line immunosuppressive treatment (EVER-ILD): A double-blind placebo-controlled randomized trial. *Respiratory medicine and research*. 2020;78:100770. doi:https://dx.doi.org/10.1016/j.resmer.2020.100770
3. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku Journal of Experimental Medicine*. 2016;239(4):279-305. doi:https://dx.doi.org/10.1620/tjem.239.297
4. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Seminars in arthritis and rheumatism*. 2017;46(5):625-631. doi:https://dx.doi.org/10.1016/j.semarthrit.2016.10.003
5. Narvaez J, Robles-Perez A, Molina-Molina M, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. *Seminars in arthritis and rheumatism*. 2020;50(5):902-910. doi:https://dx.doi.org/10.1016/j.semarthrit.2020.08.008
6. Bauhammer J, Blank N, Max R, et al. Rituximab in the Treatment of Jo1 Antibody-associated Antisynthetase Syndrome: Anti-Ro52 Positivity as a Marker for Severity and Treatment Response. *The Journal of rheumatology*. 2016;43(8):1566-74. doi:https://dx.doi.org/10.3899/jrheum.150844
7. Fui A, Bergantini L, Selvi E, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Internal medicine journal*. 2020;50(3):330-336. doi:https://dx.doi.org/10.1111/imj.14306

8. Ebata S, Yoshizaki A, Fukasawa T, et al. Rituximab therapy is more effective than cyclophosphamide therapy for Japanese patients with anti-topoisomerase I-positive systemic sclerosis-associated interstitial lung disease. *The Journal of dermatology*. 2019;46(11):1006-1013. doi:https://dx.doi.org/10.1111/1346-8138.15079

PICO 117: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 117-1. PICO 117: Excluded Studies

Reference	Reason for exclusion
Fernandez-Diaz et al. 2021[1]	No intervention of interest

References

1. Fernandez-Diaz C, Atienza-Mateo B, Castaneda S, et al. Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. *Rheumatology (Oxford, England)*. 2021;61(1):299-308. doi:https://dx.doi.org/10.1093/rheumatology/keab317

PICO 118: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 118, we provide indirect evidence from PICO 55 (JAK inhibitors compared to mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 55.

Key findings: indirect evidence from 2 observational studies (Fan 2022, Tardella 2022)

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5 associated ILD.
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 55.

References for Included Studies for PICO 55

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w

PICO 119: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding nintedanib compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 119-1. PICO 119: Excluded Studies

Reference	Reason for exclusion
Matteson et al. 2022[1]	No comparator of interest
Wells et al. 2020[2]	No comparator of interest
Kuwana et al. 2021[3]	No intervention of interest
Kuwana et al. 2021[4]	No intervention of interest
Flaherty et al. 2019[5]	No comparator of interest
Flaherty et al. 2022[6]	No comparator of interest

References

1. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075
2. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *The Lancet Respiratory medicine*. 2020;8(5):453-460. doi:https://dx.doi.org/10.1016/S2213-2600(20)30036-9
3. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern rheumatology*. 2021;31(1):141-150. doi:https://dx.doi.org/10.1080/14397595.2020.1751402
4. Kuwana M, Allanore Y, Denton CP, et al. Nintedanib in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Subgroup Analyses by Autoantibody Status and Modified Rodnan Skin Thickness Score. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(3):518-526. doi:https://dx.doi.org/10.1002/art.41965
5. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681

6. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020

PICO 120: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 121: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 122: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 123: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 124: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 124, we provide indirect evidence from PICO 25 (mycophenolate vs no mycophenolate as first line ILD treatment) and PICO 41 (plasma exchange vs no plasma exchange as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low for PICO 25 and Very low for PICO 41. An additional downgrade due to indirect comparison for PICO 124 resulted in a rating of Very low (for mycophenolate) to Very low (for plasma exchange).

Key Findings from PICO 25: direct evidence from 3 studies (2 RCTs, 1 observational study), indirect evidence from 1 observational study:

- Regarding pulmonary function, one RCT compared MMF vs. placebo and showed no difference in change in % predicted FVC at 6 months (MMF used at 2g/day). Another study using FVC changes in the SLS-II study, after controlling for baseline % predicted FVC and baseline whole lung QILD score, treatment with MMF (target dose of 1500mg BID) was associated with improved % predicted FVC over 24 months. An observational study showed worse PFT results over time for those on MMF; however, there was confounding by indication.
- Regarding safety, a double-blind RCT comparing MMF and placebo found no significant difference in the rate of adverse events (any) between the treatment and control groups. In SLS-I/SLS-II analysis, there were numerically more serious adverse events in the placebo group compared to the MMF-treated patients (30 in placebo vs. 27 in the MMF arm). There were 5 deaths in the MMF arm and 6 deaths in the placebo arm, which was not significantly different. Regarding any non-serious adverse events, there were 7 in the placebo arm and 23 in the MMF arm.

Key Findings from PICO 41: indirect evidence from 1 observational study

- Evidence from one observational study indicated improved survival at 1 year with plasma exchange (PE) vs without PE in clinically amyopathic dermatomyositis (CADM) patients with refractory ILD.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 25 and PICO 41.

Table 124-1. PICO 124 Excluded Studies

Reference	Reason for Exclusion
Hoffman-Vold et al., 2022[1]	Wrong design

References for PICO 124

1. Hoffmann-Vold AM, Volkmann ER, Allanore Y, et al. Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials. *The Lancet Rheumatology*. 2022;4(10):e679-e687.

References for Included Studies for PICO 25

1. Naidu GSRSNK, Sharma SK, Adarsh MB, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatology international*. 2020;40(2):207-216.
2. Adler S, Huscher D, Allanore Y, et al. Use of immunosuppressants in SSc patients with interstitial lung disease - Results of the deSScipher project of the eustar group. *Clinical and Experimental Rheumatology*. 2014;32(2 SUPPL. 81):S85-S86.
3. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis & rheumatology (Hoboken, NJ)*. 2017;69(7):1451-1460.
4. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2022

References for Included Studies for PICO 41

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7.

PICO 125: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 126: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 127: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding azathioprine compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective study indicated a similar rate of adverse events among patients treated with azathioprine and those treated with rituximab; however, the number of events was very small.
    - Evidence from the same study indicated a higher rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with rituximab (12 [13.0%] vs. 1 [3.9%] at 12 months of follow-up, respectively).

Summary: The literature searches identified one study that indirectly addressed this PICO question. FVC% had similar results for both AZA and RTX, and DLCO% in RTX group (6.73% in RTX group vs 1.93% in AZA group). Adverse events overall were similar between the groups; however, the rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with rituximab.

Table 127-1. PICO 127: Add Azathioprine Compared to Adding Anti-CD20 Antibody

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Treatments	Results
Matson et al., 2022[1]	Retrospective cohort study	High	212 patients diagnosed with RA-ILD	Initial treatments with Azathioprine vs. Rituximab	**FVC % predicted at 12 months**: Azathioprine 3.84%; Rituximab 3.26% **DLCO % predicted at 12 months**: Azathioprine 1.93%; Rituximab 6.73% **Adverse events (AEs):** All AE: Azathioprine 18 (19.6%); Rituximab 5 (11.6%) GI upset: Azathioprine 3 (3.3%); Rituximab 1 (2.3%)

					Elevated liver enzymes: Azathioprine 3 (3.3%); Rituximab 0 Cytopenia: Azathioprine 3 (3.3%); Rituximab 1 (2.3%) Recurrent infections: Azathioprine 4 (4.3%); Rituximab 1 (2.3%) Non-specific symptoms: Azathioprine 5 (5.4%); Rituximab 2 (4.7%) Treatment stopped due to adverse events: Azathioprine 12 (13.0%); Rituximab 1 (2.3%).

References

1. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org

PICO 128: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 128, we provide indirect evidence from PICO 65 (cyclophosphamide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Low to Very low for PICO 65. An additional downgrade due to indirect population for PICO 128 resulted in a rating of Very low.

Key Findings from PICO 65: direct evidence from 2 studies (1 RCT and 1 observational):

- One observational study found no difference in IMPORTANT outcomes KL-6 levels, %FVC, %DLCO, total GGO score, and total fibrosis score at 12 months follow-up between a very small number (n=18 per group) of individuals in the AZA and TAC groups. The study suggested that the rates of evolution of total fibrosis score, and those corrected by disease duration for 36 months follow-up, were significantly lower in the TAC group than in the AZA group (p=0.17 and 0.25, respectively). However, there was a high dropout rate—39% in the TAC group and 33% in the AZA group.
- Adverse events were reported poorly (CRITICAL outcomes):
  - Only two patients developed an infection in each group.
  - 3 (17%) patients developed mild renal injury at 12 months of follow-up in the TAC group.
  - 2 (11%) developed mild leukopenia in the AZA group.
- One observational study concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 65.

Table 0--1. PICO 128: Excluded Studies

Reference	Reason for exclusion
Li et al., 2022[1]	No comparator of interest
Tomiyama et al., 2016[2]	No comparator of interest
Goldin et al., 2008[3]	No comparator of interest
Langlois et al., 2020[4]	No intervention of interest

References

1. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases complicated with dermatomyositis: A retrospective analysis. *Medicine*. 2022;101(24):e29108. doi:https://dx.doi.org/10.1097/MD.0000000000029108

2. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku Journal of Experimental Medicine*. 2016;239(4):279-305. doi:https://dx.doi.org/10.1620/tjem.239.297

3. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367. doi:https://dx.doi.org/10.1378/chest.07-2444

4. Langlois V, Gillibert A, Uzunhan Y, et al. Rituximab and Cyclophosphamide in Antisynthetase Syndrome-related Interstitial Lung Disease: An Observational Retrospective Study. *The Journal of rheumatology*. 2020;47(11):1678-1686. doi:https://dx.doi.org/10.3899/jrheum.190505

PICO 129: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 130: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 130, we provide indirect evidence from PICO 67 (TNF inhibitors vs anti-CD20 antibody as first line ILD treatment). The certainty of evidence across all critical outcomes was rated Very low for PICO 67.

Key Findings from PICO 67: direct evidence from 1 observational study and indirect evidence from 1 observational study:

- One small observational cohort study of patients with RA-ILD suggested all-cause mortality rates per 1000 person-years (pyrs) were 53.0 (95% CI: 22.9 to 104.6) for rituximab (N=43) and 94.8 (95% CI: 74.7 to 118.7) for TNFi (N=309). This study suggested similar rates for RA-ILD as the underlying cause of death (14% [one patient] rituximab-treated vs. 16% [12 patients] TNFi-treated); however, the study was not powered to detect the difference.
- One single-center retrospective cohort study assessed the risk of infection of patients receiving TNFi (alone or in combination with any other antirheumatic drug) (n=59) vs. non-TNFI biologic (rituximab and abatacept) (n=38). The infection rate in the TNFi group vs. non-TNFI biologic group was 1.8 vs. 13.5 per 100 person-year (py), respectively.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 67.

Table 130-1. PICO 130: Excluded Studies

Reference	Reason for exclusion
Fernandez-Diaz et al., 2021[1]	No intervention of interest

References

1. Fernandez-Diaz C, Atienza-Mateo B, Castaneda S, et al. Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. *Rheumatology (Oxford, England)*. 2021;61(1):299-308. doi:https://dx.doi.org/10.1093/rheumatology/keab317

References for Included Studies for PICO 67

1. Druce KL, Iqbal K, Watson KD, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. *RMD open*. 2017;3(1):e000473. doi:https://dx.doi.org/10.1136/rmdopen-2017-000473
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

PICO 131: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 132: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 133: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 133, we provide indirect evidence from PICO 70 (JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 70.

Key Findings: direct evidence from 1 observational study (Cronin 2021)

- Evidence from one observational study suggested no difference in the respiratory events rate (i.e., composite outcome of hospitalizations and death rate) between patients with a history of JAK inhibitors and rituximab (HR 1.38, [95% CI: 0.36 to 5.28]); however, the sample size and the event rate were very small.
- One observational study found no association between the type of pharmacotherapy and drug discontinuation rate (unadjusted HR 1.90, [95% CI: 0.63 to 5.73]); however, the sample size and the event rate were very small.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 70.

Table 133-1. PICO 133: Excluded Studies

References	Reasons for exclusion
Fan et al., 2022[1]	No comparator of interest

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 134: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding nintedanib compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 134: Excluded Studies

Reference	Reason for exclusion
Tomiyama et al., 2016[1]	No intervention of interest
Daoussis et al., 2017[2]	No intervention of interest
Narvaez et al., 2020[3]	No comparator of interest
Bauhammer et al., 2016[4]	No comparator of interest
Fui et al., 2020[5]	No comparator of interest
Ebata et al., 2019[6]	No comparator of interest
Zhu et al., 2021[7]	No comparator of interest

References

1. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku Journal of Experimental Medicine*. 2016;239(4):279-305. doi:https://dx.doi.org/10.1620/tjem.239.297

2. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Seminars in arthritis and rheumatism*. 2017;46(5):625-631. doi:https://dx.doi.org/10.1016/j.semarthrit.2016.10.003

3. Narvaez J, Robles-Perez A, Molina-Molina M, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. *Seminars in arthritis and rheumatism*. 2020;50(5):902-910. doi:https://dx.doi.org/10.1016/j.semarthrit.2020.08.008

4. Bauhammer J, Blank N, Max R, et al. Rituximab in the Treatment of Jo1 Antibody-associated Antisynthetase Syndrome: Anti-Ro52 Positivity as a Marker for Severity and Treatment Response. *The Journal of rheumatology*. 2016;43(8):1566-74. doi:https://dx.doi.org/10.3899/jrheum.150844

5. Fui A, Bergantini L, Selvi E, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Internal medicine journal*. 2020;50(3):330-336. doi:https://dx.doi.org/10.1111/imj.14306

6. Ebata S, Yoshizaki A, Fukasawa T, et al. Rituximab therapy is more effective than cyclophosphamide therapy for Japanese patients with anti-topoisomerase I-positive systemic sclerosis-associated interstitial lung disease. *The Journal of dermatology*. 2019;46(11):1006-1013. doi:https://dx.doi.org/10.1111/1346-8138.15079

7. Zhu L, Chung MP, Gagne L, et al. Rituximab Versus Mycophenolate in the Treatment of Recalcitrant Connective Tissue Disease-Associated Interstitial Lung Disease. *ACR open rheumatology*. 2021;3(1):3-7. doi:https://dx.doi.org/10.1002/acr2.11210

PICO 135: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 136: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 137: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 137, we provide indirect evidence from PICO 74 (oral prednisone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for PICO 74.

Key Findings from PICO 74: indirect evidence from 1 observational study

- 1 observational study reported the following infection rates per 100 person-years:
  - 15.4 for prednisone >10 mg/day
  - 13.5 for non-TNFI biologics (abatacept or rituximab)
  - 11 for prednisone ≤10 mg/day

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 74.

References for Included Studies for PICO 74

1. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

PICO 138: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 139: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 139-1. PICO 139 Excluded Studies

Reference	Reason for Exclusion
Hoffmann-Vold et al., 2022[1]	No intervention of interest
Komai et al., 2021[2]	No intervention of interest

References

1. Hoffmann-Vold AM, Volkmann ER, Allanore Y, et al. Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials. *The Lancet Rheumatology*. 2022;4(10):e679-e687. doi:https://protect-us.mimecast.com/s/cq22CADmJpCNvoljT2Eb4ry?domain=dx.doi.org

2. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7. doi:https://dx.doi.org/10.1080/03009742.2021.1995984

PICO 140: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 141: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 142: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 142: Excluded Studies

Reference	Reason for exclusion
Li et al., 2022[1]	No comparator of interest
Tomiyama et al., 2016[2]	No outcomes of interest
Goldin et al., 2008[3]	No intervention of interest

References

1. Li L, Li M, Li Y, Wang K, Xu S. Combination therapy of tacrolimus, high doses of glucocorticosteroids, and cyclophosphamide against existing historical treatment for patients in severe conditions of interstitial lung diseases complicated with dermatomyositis: A retrospective analysis. *Medicine*. 2022;101(24):e29108. doi:https://dx.doi.org/10.1097/MD.0000000000029108

2. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku Journal of Experimental Medicine*. 2016;239(4):279-305. doi:https://dx.doi.org/10.1620/tjem.239.297

3. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367. doi:https://dx.doi.org/10.1378/chest.07-2444

PICO 143: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 143, we provide indirect evidence from PICO 80 (calcineurin inhibitors vs azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 80.

Key Findings: direct evidence from 2 observational studies

- Kiboshi et al. 2022[1] found no difference in IMPORTANT outcomes KL-6 levels, %FVC, %DLCO, total GGO score, and total fibrosis score at 12 months follow-up between a very small number (n=18 per group) of individuals in the AZA and TAC groups. The study suggested that the rates of evolution of total fibrosis score, and those corrected by disease duration for 36 months follow-up, were significantly lower in the TAC group than in the AZA group (p=0.17 and 0.25, respectively). However, there was a high dropout rate—39% in the TAC group and 33% in the AZA group.
- Adverse events were reported poorly (CRITICAL outcomes):
  - Only two patients developed an infection in each group.
  - 3 (17%) patients developed mild renal injury at 12 months of follow-up in the TAC group.
  - 2 (11%) developed mild leukopenia in the AZA group.
- Chen et al. 2022 concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 80.

Table 143-1. PICO 143: Excluded Studies

Reference	Reason for exclusion
Wilkes et al., 2005[2]	No comparator of interest

References

1. Kiboshi T, Kotani T, Konma J, et al. Comparison of therapeutic effects of combination therapy with prednisolone and tacrolimus or azathioprine on progressive interstitial pneumonia with systemic sclerosis. Modern rheumatology. 2022;32(2):358-364. doi:https://dx.doi.org/10.1080/14397595.2021.1918864

2. Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. *Arthritis and rheumatism*. 2005;52(8):2439-46.

PICO 144: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 144, we provide indirect evidence from PICO 81 (TNF inhibitors compared to azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 81.

Key findings from PICO 81: indirect evidence from 2 observational studies:

- An adjusted mortality rate ratio of 0.81, 95% CI: 0.38 to 1.73 for the TNFi RA-ILD cohort vs. the csDMARD RA-ILD cohort (based on data from the British Society for Rheumatology Biologics Register [BSRBR])
- No significant difference between RA-ILD patients on TNFis that were categorized as progressive RA-ILD (15.6%) vs. stable RA-ILD (34.9%).

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 81.

References for Included Studies for PICO 81

1. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Annals of rheumatic diseases*. 2010;69(6):1086-91. doi:https://dx.doi.org/10.1136/ard.2009.120626
2. Chen N, Diao C-Y, Gao J, Zhao D-B. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Seminars in arthritis and rheumatism*. 2022;55:152004. doi:https://dx.doi.org/10.1016/j.semarthrit.2022.152004

PICO 145: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 146: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 146: Excluded Studies

Reference	Reason for exclusion
Fernandez-Diaz et al., 2021[1]	No comparator of interest

References

1. Fernandez-Diaz C, Atienza-Mateo B, Castaneda S, et al. Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. *Rheumatology (Oxford, England)*. 2021;61(1):299-308. doi:https://dx.doi.org/10.1093/rheumatology/keab317

PICO 147: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 147, we provide indirect evidence from PICO 84 (JAK inhibitors compared to azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 84.

Key findings from PICO 84: indirect evidence from 2 observational studies

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5 associated ILD.[1]
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.[2]

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 84.

Table 147-1. PICO 147: Excluded Studies

Reference	Reason for exclusion
Fan et al., 2022[1]	Wrong study design

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 148: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding nintedanib compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 148: Excluded Studies

Reference	Reason for exclusion
Matteson et al., 2022[1]	No comparator of interest
Wells et al., 2020[2]	No population of interest
Flaherty et al., 2019[3]	No comparator of interest
Flaherty et al., 2022[4]	No comparator of interest

References

1. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075

2. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *The Lancet Respiratory medicine*. 2020;8(5):453-460. doi:https://dx.doi.org/10.1016/S2213-2600(20)30036-9

3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681

4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020

PICO 149: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 150: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 151: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 152: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 153: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 153-1. PICO 153 Excluded Studies

Reference	Reason for Exclusion
Hoffmann-Vold et al., 2022[1]	No intervention of interest
Komai et al., 2021[2]	No intervention of interest

References

1. Hoffmann-Vold AM, Volkmann ER, Allanore Y, et al. Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials. *The Lancet Rheumatology*. 2022;4(10):e679-e687. doi:https://protect-us.mimecast.com/s/cq22CADmJpCNvoljT2Eb4ry?domain=dx.doi.org

2. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7. doi:https://dx.doi.org/10.1080/03009742.2021.1995984

PICO 154: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 154, we provide indirect evidence from PICO 91 (methotrexate compared to cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very Low for PICO 91.

Key Findings from PICO 91: indirect evidence from 1 observational study

- 28 (27.1%) patients classified as "progressive" and 32 (39.5%) patients classified as "stable" were taking methotrexate (p=0.08), while 38 (36.8%) patients classified as "progressive" and 43 (53.1%) patients classified as "stable" were taking cyclophosphamide (p=0.04).
- Treatment with cyclophosphamide was associated with better survival (HR 0.43, 95% CI: 0.26 to 0.69; p<0.01).

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 91.

References for Included Studies for PICO 91

1. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clinical rheumatology*. 2019;38(4):1109-1116. doi:https://dx.doi.org/10.1007/s10067-018-4382-x

PICO 155: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 156: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 156: Excluded Studies

Reference	Reason for exclusion
Li et al., 2022[1]	No comparator of interest
Grau et al., 1996[2]	No outcomes of interest
Wilkes et al., 2005[3]	No comparator of interest

PICO 157: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 158: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 159: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 159: Excluded Studies

Reference	Reason for exclusion
Fernandez-Diaz et al., 2021[1]	No comparator of interest

References

1. Fernandez-Diaz C, Atienza-Mateo B, Castaneda S, et al. Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. *Rheumatology (Oxford, England)*. 2021;61(1):299-308. doi:https://dx.doi.org/10.1093/rheumatology/keab317

PICO 160: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 160, we provide indirect evidence from PICO 97 (JAK inhibitors compared to cyclophosphamide as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 97.

Key findings from PICO 97: indirect evidence from 2 observational studies

- One retrospective observational study (Fan et al., 2022)[1] found that among patients with MDA5-related interstitial lung disease, treatment with tofacitinib was associated with lower 6-month (p=0.03) and 12-month (p=0.03) mortality when compared to treatment with tacrolimus.
  - This association was maintained at 12-months after adjustment for age, sex, smoking history, MDA5 titer and concurrent medication use (HR 0.44; 95% CI 0.20-0.96; p=0.04).
- A second retrospective observational study (Tardella et al., 2022) [2] found that among patients with RA-ILD with ≥10% extent of fibrosis on HRCT, treatment with a JAK inhibitor (either tofacitinib or baricitinib) was associated with a nominally lower risk of ILD progression on HRCT (16.1% vs 11.3%).
  - ILD progression on HRCT was measured quantitatively
  - Inference testing was not performed between treatment groups

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 97.

Table 160-1. PICO 160: Excluded Studies

Reference	Reason for Exclusion
Fan et al., 2022[1]	No comparator of interest

References

1. Fan L, Lyu W, Liu H, Jiang H, Chen L, Liu Y, Zhuang Y, Huang M, Cao M, Cai H, Xiao Y, Dai J. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. J Rheumatol. 2022;49(12):1356-64. Epub 20220815. doi: 10.3899/jrheum.220367. PubMed PMID: 3597052

References for Included Studies for PICO 97

2. Fan L, Lyu W, Liu H, Jiang H, Chen L, Liu Y, Zhuang Y, Huang M, Cao M, Cai H, Xiao Y, Dai J. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. J Rheumatol. 2022;49(12):1356-64. Epub 20220815. doi: 10.3899/jrheum.220367. PubMed PMID: 3597052
3. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w
4.

PICO 161: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding nintedanib compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 161: Excluded Studies

Reference	Reason for exclusion
Matteson et al., 2022[1]	No comparator of interest
Wells et al., 2020[2]	Population not of interest
Flaherty et al., 2019[3]	No comparator of interest
Flaherty et al., 2022[4]	No comparator of interest

References

1. Matteson EL, Kelly C, Distler JHW, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. *Arthritis & rheumatology (Hoboken, NJ)*. 2022;74(6):1039-1047. doi:https://dx.doi.org/10.1002/art.42075

2. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *The Lancet Respiratory medicine*. 2020;8(5):453-460. doi:https://dx.doi.org/10.1016/S2213-2600(20)30036-9

3. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *The New England journal of medicine*. 2019;381(18):1718-1727. doi:https://dx.doi.org/10.1056/NEJMoa1908681

4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *European Respiratory Journal*. 2022;59(3):2004538. doi:https://dx.doi.org/10.1183/13993003.04538-2020

PICO 162: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 163: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 164: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 164, we provide indirect evidence from PICO 101 (oral prednisone vs cyclophosphamide as first line ILD treatment). The certainty of evidence across all critical outcomes was rated Very low for PICO 101.

Key Findings from PICO 101: indirect evidence from 1 RCT (comparing IV cyclophosphamide (CYC) with a combination of CYC plus prednisone (PRED)

- After 12 months of treatment, there was no improvement in PFTs (FVC, FEV1, and DLCO) in both groups, and they remained stable at 1 and 3 years.
- CYC was effective in stabilizing lung function in NSIP pattern of lung disease for 3 years after 1-year treatment with CYC. The association of PRED did not bring further improvement with regard to lung fibrosis.
- Therapy was well tolerated, with no patient developing scleroderma renal crisis in the CYC+PRED group.

For additional information, please see the Executive Summary, and data provided in SOF/Word tables under PICO 101.

Table 0-1:PICO 4: Excluded Studies

Reference	Reason for exclusion
Li et al., 2019[1]	No population of interest

References

1. Li J, Chen X, Qu Y. Effects of cyclophosphamide combined with prednisone on TNF-alpha expression in treatment of patients with interstitial lung disease. *Experimental and therapeutic medicine*. 2019;18(6):4443-4449. doi:https://dx.doi.org/10.3892/etm.2019.8099

References for Included Studies for PICO 101

1. Domiciano DS, Bonfa E, Borges CTL, et al. A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma. *Clinical rheumatology*. 2011;30(2):223-9. doi:https://dx.doi.org/10.1007/s10067-010-1493-4

PICO 165: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 166: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 166-1. PICO 166: Excluded Studies

Reference	Reason for Exclusion
Komai et al., 2021[1]	Wrong population
Bay et al., 2022[2]	Wrong Population
Hoffmann-Vold et al., 2022[3]	No intervention of interest

References

1. Komai T, Iwasaki Y, Tsuchida Y, et al. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scandinavian journal of rheumatology*. 2021:1-7. doi:https://dx.doi.org/10.1080/03009742.2021.1995984

2. Bay P, e Chambrun MP, Rothstein V, et al. Efficacy of plasma exchange in patients with anti-MDA5 rapidly progressive interstitial lung disease. *Journal of autoimmunity*. 2022;133:102941. doi:https://protect-us.mimecast.com/s/Yx-rCPNY2LiK7mNQhrKs7Q0?domain=dx.doi.org

3. Hoffmann-Vold AM, Volkmann ER, Allanore Y, et al. Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials. *The Lancet Rheumatology*. 2022;4(10):e679-e687. doi:https://protect-us.mimecast.com/s/cq22CADmJpCNvoljT2Eb4ry?domain=dx.doi.org

PICO 167: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of referral for stem cell transplant compared to optimal medical management on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 167: Excluded Studies

Reference	Reason for exclusion
Henrique-Neto et al., 2021[1]	No comparator of interest
Kloth et al., 2016[2]	No comparator of interest

References

1. Henrique-Neto A, Vasconcelos MYK, Dias JBE, et al. Hematopoietic stem cell transplantation for systemic sclerosis: Brazilian experience. *Advances in rheumatology (London, England)*. 2021;61(1):9. doi:https://dx.doi.org/10.1186/s42358-021-00166-8

2. Kloth C, Maximilian Thaiss W, Preibsch H, et al. Quantitative chest CT analysis in patients with systemic sclerosis before and after autologous stem cell transplantation: comparison of results with those of pulmonary function tests and clinical tests. *Rheumatology (Oxford, England)*. 2016;55(10):1763-70. doi:https://dx.doi.org/10.1093/rheumatology/kew259

PICO 168: In rheumatic disease patients with ILD progression after 1st ILD therapy, what is the impact of referral for lung transplant compared to optimal medical management on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes**: Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 168: Excluded Studies

Reference	Reason for exclusion
Chizinga et al., 2022[1]	No comparator of interest

References

1. Chizinga M, Machuca TN, Shahmohammadi A, et al. Lung transplantation for acute exacerbation of interstitial lung disease. *Thorax*. 2022;77(4):364-369. doi:https://dx.doi.org/10.1136/thoraxjnl-2020-215681

PICO 169: In rheumatic disease patients with rapidly progressive ILD, what is the impact of daily oral prednisone compared to no daily oral prednisone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 170: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pulse intravenous glucocorticoids compared to no pulse intravenous glucocorticoids as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 171: In rheumatic disease patients with rapidly progressive ILD, what is the impact of nintedanib compared to no nintedanib as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 171 Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	No outcomes of interest

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 172: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pirfenidone compared to no pirfenidone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 172 Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	No outcomes of interest

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 173: In rheumatic disease patients with rapidly progressive ILD, what is the impact of adding nintedanib to mycophenolate compared to not adding nintedanib to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 173, we provide indirect evidence from PICO 107 (adding combination of nintedanib and mycophenolate compared to adding mycophenolate alone after 1st ILD therapy) below. The certainty of evidence across all critical outcomes was rated Very low to low for PICO 107.

Key Findings from PICO 107: indirect evidence from 1 RCT (Highland et al. 2021)

A subgroup analysis of 279 individuals taking mycophenolate in the SENSCIS trial (nintedanib vs. placebo) indirectly addresses PICO 107. At 52 weeks follow-up, no significant difference was reported in the annual rate of decline in FVC (difference 26.3, 95% CI: -27.9 to 80.6) or change in SGRQ total score (1.6, 95% CI: -1.86 to 5.06). The rate of composite adverse event outcome did not differ between the groups.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 107.

References for PICO 107

1. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *The Lancet Respiratory medicine*. 2021;9(1):96-106. doi:https://dx.doi.org/10.1016/S2213-2600(20)30330-1
2. Allanore Y, Vonk MC, Distler O, et al. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Annals of the rheumatic diseases*. 2022;81(12):1722-1729. doi:https://protect-us.mimecast.com/s/7ceMCo2ON1fr7GPkHwiRPo?domain=dx.doi.org

PICO 174: In rheumatic disease patients with rapidly progressive ILD, what is the impact of adding pirfenidone to mycophenolate compared to not adding pirfenidone to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 175: In rheumatic disease patients with rapidly progressive ILD, what is the impact of upfront combination of nintedanib with mycophenolate compared to mycophenolate alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 176: In rheumatic disease patients with rapidly progressive ILD, what is the impact of upfront combination of pirfenidone with mycophenolate compared to mycophenolate alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 177: In rheumatic disease patients with rapidly progressive ILD, what is the impact of methotrexate compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 177 Excluded Studies

Reference	Reason for exclusion
Tille-Leblond et al., 2008[1]	No comparator of interest

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

PICO 178: In rheumatic disease patients with rapidly progressive ILD, what is the impact of leflunomide compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 179: In rheumatic disease patients with rapidly progressive ILD, what is the impact of azathioprine compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from two retrospective studies among patients without RP-ILD (i.e., indirect evidence) suggests that there is no difference between adding azathioprine compared to adding mycophenolate on disease-related outcomes (i.e., FCV%, DLCO%, at 6- and 12-months of follow-up).
- Evidence from two retrospective studies among patients without RP-ILD (i.e., indirect evidence) suggests a similar rate of adverse events among patients treated with azathioprine and those treated with mycophenolate; however, the number of events was very small.
    - Evidence from one study[1] indicated a 3-fold higher rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with mycophenolate (12 [13.0%] vs. 3 [3.9%] at 12 months of follow-up, respectively).

Summary:

We included two studies with indirect evidence for patient population—participants in these studies had no rapidly progressive ILD.

We included two very low-quality studies that compared physiologic and drug adverse events (i.e., toxicity) among 46 patients with Polymyositis/ Dermatomyositis (PM/DM-ILD)[2] and 212 patients with RA-ILD.[1] The study found no statistically significant difference in FVC % predicted at 6 and 12 months, DLCO % predicted at 6 and 12 months, and medication toxicity between those given azathioprine compared to those given mycophenolate mofetil (see Table 111-1). But the other study shows that FVC% and DLCO% predicted were both higher in patients taking MMF and that adverse events are higher in patients taking AZA.

Table 179-1. PICO 179: Add Azathioprine Compared to Adding Mycophenolate after 1st ILD therapy

Author, year	Study design	Risk of bias	Follow-up	Population Description	Treatment: Comparator:	Results
Mira-Avenado, et al., 2013[2]	Retrospective	High due to	6 and 12 months	**Number of patients**: 46	CYC (n=24, average dose 129 mg daily),	**FVC% (median, IQR)** ***6 months***

		immortal time bias		**Age**: 50–56 years **Gender**: men (20) women (26) **Diagnosis:** Polymyositis (PM)/ dermatomyositis (DM) associated ILD who required steroid sparing agent after high dose GC due to persistent lung disease or significant symptoms and abnormal PFT; required to have longitudinal follow-up for at least 6 months **Associated disease:** PM: 74%; DM: 26%	AZA (n=13, avg dose 130 mg daily) or MMF (n=9, avg dose 2.2 g daily) after steroids; treatment selected at discretion of treating MD ***Note***: 13 patients switched therapy at 6 months (toxicity 2, potential toxicity 6, inadequate response 5) - 10 on CYC (4 to AZA, 6 to MMF), 2 on AZA (2 to CYC), 1 on MMF (1 to AZA); unclear how these were analyzed.	AZA 59 (53 to 80) MMF 67 (57 to 90) ***12 months*** AZA 61 (52 to 85) MMF 64 (52 to 81) **DLCO% (median, IQR)** ***6 months*** (median, IQR) AZA 54 (44 to 65) MMF 64 (58 to 69) ***12 months*** (median IQR) AZA 61 (38 to 74) MMF 63 (50 to 64) **Toxicity** AZA 3 (23%) MMF 4 (44%)
Matson et al., 2022[1]	Retrospective cohort study	High	Median follow-up period of 33months	212 patients diagnosed with RA-ILD	Azathioprine Mycophenolate	**FVC % predicted at 12 months**: Azathioprine 3.34%; Mycophenolate 4.55% **DLCO % predicted at 12 months**: Azathioprine 1.93%; Mycophenolate 3.67% **Adverse events (AEs):** All AE: Azathioprine 18 (19.6%); Mycophenolate 12 (15.6%) GI: Azathioprine 3 (3.3%); Mycophenolate 5 (6.5%)

						Elevated liver enzymes: Azathioprine 3 (3.3%); Mycophenolate 0 % Cytopenia: Azathioprine 3 (3.3%); Mycophenolate 2 (2.6%) Recurrent infections: Azathioprine 4 (4.3%); Mycophenolate 2 (2.6%) Non-specific symptoms: Azathioprine 5 (5.4%); Mycophenolate 3 (3.9%) Treatment stopped due to adverse event: Azathioprine 12 (13.0%); Mycophenolate 3 (3.9%)

AZA: azathioprine; CYC: cyclophosphamide; DLCO: diffusing capacity for carbon monoxide; DM: dermatomyositis; FVC: forced vital capacity; MMF: mycophenolate mofetil; PM: polymyositis; ROB: risk of bias

Table 0-1. PICO 179 Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[3]	No comparator of interest

References

1. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022;doi:https://protect-us.mimecast.com/s/H-hZCJ6PVBtq7zAxuG5lK0Y?domain=dx.doi.org
2. Mira-Avendano IC, Parambil JG, Yadav R, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respiratory medicine*. 2013;107(6):890-6. doi:https://dx.doi.org/10.1016/j.rmed.2013.02.015
3. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

PICO 180: In rheumatic disease patients with rapidly progressive ILD, what is the impact of cyclophosphamide compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 180, we provide indirect evidence from PICO 49 (cyclophosphamide vs mycophenolate as first line ILD treatment) and PICO 112 (adding cyclophosphamide vs adding mycophenolate after 1st ILD therapy). The certainty of evidence across all critical outcomes was rated Low to Very low for PICO 49 and Very low for PICO 112. An additional downgrade due to indirect comparison for PICO 180 resulted in a rating of Very low.

Key Findings from PICO 49: direct evidence from 3 studies (1 RCT and 2 observational):

- Evidence from one RCT (Scleroderma Lung Study II [SLS II]) suggested no difference in the risk of all-cause mortality, SSc-related mortality, and time to death among those in the CYC and MMF groups at follow-up up to 2 years; however, the study was not powered to detect mortality differences (low quality of evidence).
- Evidence from one RCT (SLS II) suggested no difference in the number of individuals meeting minimum clinically important difference (MCID) for quality of life at 12 and 24 months of follow-up (low quality of evidence).
- Evidence from one RCT (SLS II) suggested no difference in the number of individuals meeting MCID for disability at 12 and 24 months of follow-up (low quality of evidence).
- Evidence from the SLS II trial suggested no difference between the groups for Transitional Dyspnea Index and St. George's Respiratory Questionnaire (SGRQ) (among individuals who met or exceeded minimal clinically important difference) at 12 and 24 months of follow-up (low quality of evidence).
- Harms:
    a. Evidence from the SLS II trial suggested a lower risk of leukopenia among individuals in the MMF group—4/69 (5.8%), compared to those in the CYC group—31/83 (37.3%). The absolute difference was 352 fewer individuals with leukopenia per 1,000 patients (95% CI: 390 fewer to 252 fewer) (low quality of evidence).
    b. Evidence from two observational studies suggested a lower risk of lower respiratory tract infection among individuals in the MMF group—5/44 (11.4%), compared to those in the CYC group—10/33 (30.3%). The absolute difference was 198 fewer cases per 1,000 (95% CI: 269 fewer to 17 fewer) (very low quality of evidence).

c. Evidence from the SLS II trial and one observational study suggested no difference between CYC and MMF and the risk of anemia, hematuria, pneumonia, thrombocytopenia, rate of serious adverse events, rate of the treatment-related composite outcome at any follow-up (low quality of evidence).

Key Findings from PICO 112: direct evidence from 1 observational study:

- Evidence from one retrospective cohort study suggests that there is no difference between adding cyclophosphamide compared to adding mycophenolate on disease-related outcomes.
- Study suggested no difference between adding cyclophosphamide compared to adding mycophenolate and the rate of treatment-related adverse events.

For additional information, please see the Executive Summaries, and data provided in Summary of Findings (SOF)/Word tables under PICO 49 and PICO 112.

Table 180-1. PICO 180: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[1]	No comparator of interest
Mao et al., 2020[2]	No comparator of interest

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237
2. Mao M-M, Xia S, Guo B-P, et al. Ultra-low dose rituximab as add-on therapy in anti-MDA5-positive patients with polymyositis /dermatomyositis associated ILD. *Respiratory medicine*. 2020;172:105983. doi:https://dx.doi.org/10.1016/j.rmed.2020.105983

References for Included Studies for PICO 49

1. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *The Lancet Respiratory medicine*. 2016;4(9):708-719. doi:https://dx.doi.org/10.1016/S2213-2600(16)30152-7

2. Volkmann ER, Tashkin DP, Sim M, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. *Annals of the rheumatic diseases*. 2019;78(1):122-130. doi:https://dx.doi.org/10.1136/annrheumdis-2018-213708
3. Volkmann ER, Tashkin DP, LeClair H, et al. Treatment With Mycophenolate and Cyclophosphamide Leads to Clinically Meaningful Improvements in Patient-Reported Outcomes in Scleroderma Lung Disease: Results of Scleroderma Lung Study II. *ACR open rheumatology*. 2020;2(6):362-370. doi:https://dx.doi.org/10.1002/acr2.11125
4. Panopoulos ST, Bournia V-K, Trakada G, Giavri I, Kostopoulos C, Sfikakis PP. Mycophenolate versus cyclophosphamide for progressive interstitial lung disease associated with systemic sclerosis: a 2-year case control study. *Lung*. 2013;191(5):483-9. doi:https://dx.doi.org/10.1007/s00408-013-9499-8
5. Tashkin DP, Volkmann ER, Tseng C-H, et al. Improved Cough and Cough-Specific Quality of Life in Patients Treated for Scleroderma-Related Interstitial Lung Disease: Results of Scleroderma Lung Study II. *Chest*. 2017;151(4):813-820. doi:https://dx.doi.org/10.1016/j.chest.2016.11.052
6. Kelly CA, Nisar M, Arthanari S, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. *Rheumatology (Oxford, England)*. 2021;60(4):1882-1890. doi:https://dx.doi.org/10.1093/rheumatology/keaa577

References for Included Studies for PICO 112

1. Mira-Avendano IC, Parambil JG, Yadav R, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respiratory medicine*. 2013;107(6):890-6. doi:https://dx.doi.org/10.1016/j.rmed.2013.02.015

PICO 181: In rheumatic disease patients with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 181-1. PICO 181: Excluded Studies

Reference	Reason for Exclusion
Kurita et al., 2015 [1]	Wrong population
Takada et al., 2020[2]	No comparator of interest

References

1. Kurita T, Yasuda S, Oba K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology (Oxford, England)*. 2015;54(1):39-44. doi:https://dx.doi.org/10.1093/rheumatology/keu166

2. Takada K, Katada Y, Ito S, et al. Impact of adding tacrolimus to initial treatment of interstitial pneumonitis in polymyositis/dermatomyositis: a single-arm clinical trial. *Rheumatology (Oxford, England)*. 2020;59(5):1084-1093. doi:https://dx.doi.org/10.1093/rheumatology/kez394

PICO 182: In rheumatic disease patients with rapidly progressive ILD, what is the impact of TNF inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 183: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 184: In rheumatic disease patients with rapidly progressive ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 184, we provide indirect evidence from PICO 116 (adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to adding mycophenolate after 1st line therapy) below. The certainty of evidence across all critical outcomes was rated Very Low for PICO 116.

Key Findings from PICO 116: indirect evidence from 1 observational study

- Evidence from one retrospective cohort study suggests that there is no difference between adding rituximab and mycophenolate compared to mycophenolate alone on disease-related outcomes except for a relative decrease in average prednisone dose in those given rituximab (RTX) with or without mycophenolate (MMF) vs. MMF alone. The rate of adverse events in the control group was not reported.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 116.

Table 0-1. PICO 184: Excluded Studies

Reference	Reason for exclusion
Mao et al., 2020[1]	No comparator of interest

References

1. Mao M-M, Xia S, Guo B-P, et al. Ultra-low dose rituximab as add-on therapy in anti-MDA5-positive patients with polymyositis /dermatomyositis associated ILD. *Respiratory medicine*. 2020;172:105983. doi:https://dx.doi.org/10.1016/j.rmed.2020.105983

References for Included Studies for PICO 116

1. Zhu L, Chung MP, Gagne L, et al. Rituximab Versus Mycophenolate in the Treatment of Recalcitrant Connective Tissue Disease-Associated Interstitial Lung Disease. *ACR open rheumatology*. 2021;3(1):3-7. doi:https://dx.doi.org/10.1002/acr2.11210

PICO 185: In rheumatic disease patients with rapidly progressive ILD, what is the impact of abatacept compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 186: In rheumatic disease patients with rapidly progressive ILD, what is the impact of JAK inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 186, we provide indirect evidence from PICO 55 (JAK inhibitors compared to mycophenolate as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 55.

Key findings: indirect evidence from 2 observational studies

- One retrospective study demonstrated that tofacitinib (TOF) may be effective for treating MDA-5 associated ILD.
- One retrospective study comparing JAK inhibitors with abatacept indicated no significant change in average DLCO, FVC, or HRCT scores after 18 months of therapy.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 55.

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org
2. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology*. 2022;30(3):705-712. doi:https://dx.doi.org/10.1007/s10787-022-00936-w

PICO 187: In rheumatic disease patients with rapidly progressive ILD, what is the impact of nintedanib compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 187: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 188: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pirfenidone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 188: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 189: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IVIG compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 190: In rheumatic disease patients with rapidly progressive ILD, what is the impact of oral prednisone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 191: In rheumatic disease patients with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 192: In rheumatic disease patients with rapidly progressive ILD, what is the impact of plasma exchange compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 193: In rheumatic disease patients with rapidly progressive ILD, what is the impact of methotrexate compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 193: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[1]	Wrong study type

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

PICO 194: In rheumatic disease patients with rapidly progressive ILD, what is the impact of leflunomide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 195: In rheumatic disease patients with rapidly progressive ILD, what is the impact of azathioprine compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- Evidence from one retrospective study among patients without RP-ILD (i.e., indirect evidence) indicated a similar rate of adverse events among patients treated with azathioprine and those treated with rituximab; however, the number of events was very small.
    - Evidence from the same study indicated a higher rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with rituximab (12 [13.0%] vs. 1 [3.9%] at 12 months of follow-up, respectively).

Summary: We identified one study with indirect evidence for patient population—participants in these studies did not have rapidly progressive ILD. FVC% had similar results for both AZA and RTX, and DLCO% in RTX group (6.73% in RTX group vs 1.93% in AZA group). Adverse events overall were similar between the groups; however, the rate of treatment discontinuation due to adverse events among patients treated with azathioprine than patients treated with rituximab.

Table 195-1. PICO 195: Azathioprine Compared to anti-CD20 antibody as first-line rapidly progressive ILD therapy

Author, year	Study type	Risk of Bias	Population Description	Treatments	Results	GRADE Certainty Rating
Matson et al., 2022[1]	Retrospective cohort study	High	212 patients diagnosed with RA-ILD	Initial treatments with Azathioprine vs. Rituximab	**FVC % predicted at 12 months**: Azathioprine 3.84%; Rituximab 3.26% **DLCO % predicted at 12 months**: Azathioprine 1.93%; Rituximab 6.73% **Adverse events (AEs):** All AE: Azathioprine 18 (19.6%); Rituximab 5 (11.6%)	Very low

					GI upset: Azathioprine 3 (3.3%); Rituximab 1 (2.3%) Elevated liver enzymes: Azathioprine 3 (3.3%); Rituximab 0 Cytopenia: Azathioprine 3 (3.3%); Rituximab 1 (2.3%) Recurrent infections: Azathioprine 4 (4.3%); Rituximab 1 (2.3%) Non-specific symptoms: Azathioprine 5 (5.4%); Rituximab 2 (4.7%) Treatment stopped due to adverse events: Azathioprine 12 (13.0%); Rituximab 1 (2.3%).	

Table 0-1. PICO 195: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[2]	Wrong study type

References

1. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest*. 2022

2. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.

PICO 196: In rheumatic disease patients with rapidly progressive ILD, what is the impact of cyclophosphamide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings

Indirect evidence from 1 RCT (Maher et al. [RECITAL] 2023[1]) with low certainty of evidence due to small sample size and imprecision suggests:

- No difference between cyclophosphamide and rituximab in mortality risk and progression-free survival among patients with connective tissue rapidly progressive ILD; however, the event rate was very small (48 weeks of follow-up).
- Fewer adverse events among participants receiving rituximab (445 events) than those receiving cyclophosphamide (646 events) (48 weeks of follow-up).
- Higher rate of gastrointestinal disorders (170 vs. 71 events), general disorders and administration site reactions (91 vs. 52 events), and nervous system disorders among patients in the cyclophosphamide group vs. rituximab (72 vs. 35) (48 weeks of follow-up).
- Similar study discontinuation rate in both groups—RR 0.54; 95% CI: 0.27 to 1.10 (48 weeks of follow-up).
- No difference in FVC, DLco, 6 min walk test, or quality of life (as measured by the EQ-5D and SGRQ) (24- and 48-week follow-up).

Summary of Evidence

One RCT randomized 101 patients to receive cyclophosphamide (n=51) or rituximab (n=48) in the treatment of connective tissue disease-associated severe or progressive ILD. At 24 weeks, FVC was improved from baseline in both the cyclophosphamide group (unadjusted mean increase 99 mL [SD 329]) and the rituximab group (97 mL [234]); in the adjusted mixed-effects model, the difference in the primary endpoint at 24 weeks was –40 mL (95% CI –153 to 74; p=0.49) between the rituximab group and the cyclophosphamide group. KBILD quality-of-life scores were improved at 24 weeks by a mean of 9.4 points (SD 20·8) in the cyclophosphamide group and 8·8 points (17.0) in the rituximab group. No significant differences in secondary endpoints were identified between the treatment groups, except for a change in GDA score at week 48, which favored cyclophosphamide (difference 0·90 [95% CI 0.11 to 1.68]). Improvements in lung function and respiratory-related quality-of-life measures were observed in both

treatment groups. Lower corticosteroid exposure over 48 weeks of follow-up was recorded in the rituximab group. Two (4%) of 48 participants who received cyclophosphamide and three (6%) of 49 who received rituximab died during the study, all due to complications of CTD or ILD. Overall survival, progression-free survival, and time to treatment failure did not significantly differ between the two groups. All participants reported at least one adverse event during the study. Numerically fewer adverse events were reported by participants receiving rituximab (445 events) than those receiving cyclophosphamide (646 events). Gastrointestinal and respiratory disorders were the most reported adverse events in both groups. There were 62 serious adverse events of which 33 occurred in the cyclophosphamide group and 29 in the rituximab group.

Table 196-1: PICO 196: Cyclophosphamide (CYC) compared to rituximab (RTX) in Rapidly Progressive ILD

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Maher, T. et al. (RECITAL) 2023[1]	2b Phase; RCT (all outcomes from this trial presented here)	Moderate (recruitment was terminated preliminary that led to study not reaching statistical power to detect the difference)	24 and 48 weeks	Adults aged 18–80 years with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD, recruited across 11 specialist ILD or rheumatology centers in the UK	Patients were randomized (1:1) to receive rituximab (n=51; 1000 mg at weeks 0 and 2 intravenously) or cyclophosphamide (n=50; 600 mg/m² body surface area every 4 weeks intravenously for six doses).	**Mortality (48 weeks)** CYC: 4% (2/48) RTX: 6% (4/49) ***No difference*** **Overall survival: hazard ratio (HR; 48 weeks):** 1.72, 95% CI: 0.31 to 9.56 **Progression-free survival: HR; 48 weeks**: 1.11; 95% CI: 0.63 to 1.99 **Treatment failure: HR; 48 weeks**: 1.25, 95% CI: 0.34 to 4.65 **Adverse events (48 weeks)** CYC: 646 events in 48 pts RTX: 445 events in 49 pts ***Not Tested (more AEs reported in the CYC group compared to RTX)*** • Gastrointestinal disorders (170 vs 71 events), general disorders and administration site reactions (91 vs 52 events) and nervous system disorders (72 *vs* 35 events) were more common in the cyclophosphamide group

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						than in the rituximab group. The rate of other AE was similar across both groups. **Study Discontinuation (48 weeks)** CYC: 9/50 RTX: 17/51 RR 0.54; 95% CI: 0.27 to 1.10, **no difference** **Carbon monoxide diffusion capacity of the lung, mL/min per kPa change** **24 weeks:** Adjusted difference: 0·186 (–0·054 to 0·425); p=0·425; ***no difference*** **48 weeks:** Adjusted difference: 0·117 (–0·137 to 0·372); p=0·372; ***no difference*** **Forced vital capacity, mL change** **24 weeks:** Adjusted difference: –40 (–153 to 74); p=0·493; ***no difference*** **48 weeks:** Adjusted difference: –58 (–178 to 62); p=0·345; ***no difference*** **Quality of Life** ED-5D **24 weeks:** Adjusted difference: 3·06 (–3·05 to 9·18) p=0·326; ***no difference*** **48 weeks:** Adjusted difference: 4·77 (–1·73 to 11·27) p=0·150; ***no difference*** KBILD Score **24 weeks:** Adjusted difference: 0·40 (–5·73 to 6·52) p=0·899; ***no difference*** **48 weeks:** Adjusted difference: 1·15 (–5·34 to 7·64) p=0·728; ***no difference*** SGRQ Score

Ref ID, Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
						24 weeks: Adjusted difference: 0·63 (–5·64 to 6·91) p=0·843; ***no difference*** **48 weeks:** Adjusted difference: 2·82 (–3·69 to 9·34) p=0·396; ***no difference***

EQ-5D=European Quality of Life Five-Dimension. KBILD=King's Brief Interstitial Lung Disease. SGRQ=St George's Respiratory Questionnaire.

Key Findings from Other Indirect Evidence (from PICO 65: 1 RCT and 1 observational)

- Evidence from one RCT (Sircar et al., 2018) suggested no difference in mortality risk among patients randomized to cyclophosphamide or rituximab at 6 months of follow-up; however, only one death occurred in each study arm (very low quality of evidence).
- Adverse events (AEs)
    - Evidence from one RCT suggested a 5.4-fold higher risk of any AEs (composite outcome) among individuals randomized to cyclophosphamide than those randomized to rituximab at 6 months of follow-up.
    - Evidence from one RCT suggested no difference between the risk of single AEs among individuals randomized to cyclophosphamide than among those randomized to rituximab at 6 months of follow-up; however, the event rate was very small (very low quality of evidence).
    - Evidence from one RCT[1] suggested no difference in the study discontinuation rate among individuals randomized to cyclophosphamide and rituximab at 6 months of follow-up; however, the event rate was very small (very low quality of evidence).

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 65.

Table 0--21. PICO 196: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[2]	Wrong study type
Mao et al., 2020[3]	No comparator of interest

References for PICO 196

1. Maher TM, Tudor VA, Saunders P, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. The Lancet Respiratory medicine. 2023;11(1):45-54.
2. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237
3. Mao M-M, Xia S, Guo B-P, et al. Ultra-low dose rituximab as add-on therapy in anti-MDA5-positive patients with polymyositis /dermatomyositis associated ILD. *Respiratory medicine*. 2020;172:105983. doi:https://dx.doi.org/10.1016/j.rmed.2020.105983

References for Included Studies for PICO 65

1. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology (Oxford, England)*. 2018;57(12):2106-2113. doi:https://dx.doi.org/10.1093/rheumatology/key213
2. Maher TM, Tudor VA, Saunders P, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. The Lancet Respiratory medicine. 2023;11(1):45-54.
3. Yilmaz DD, Borekci S, Musellim B. Comparison of the effectiveness of cyclophosphamide and rituximab treatment in patients with systemic sclerosis-related interstitial lung diseases: a retrospective, observational cohort study. *Clinical rheumatology*. 2021;40(10):4071-4079. doi:https://dx.doi.org/10.1007/s10067-021-05785-6

PICO 197: In rheumatic disease patients with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to anti-CD20 (rituximab, ocrelizumab, obinutuzumab, ofatumumab) antibody as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 198: In rheumatic disease patients with rapidly progressive ILD, what is the impact of TNF inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 198, we provide indirect evidence from PICO 67 (TNF inhibitors vs anti-CD20 antibody as first line ILD treatment). The certainty of evidence across all critical outcomes was rated Very low for PICO 67.

Key Findings from PICO 67: direct evidence from 1 observational study and indirect evidence from 1 observational study:

- One small observational cohort study of patients with RA-ILD suggested all-cause mortality rates per 1000 person-years (pyrs) were 53.0 (95% CI: 22.9 to 104.6) for rituximab (N=43) and 94.8 (95% CI: 74.7 to 118.7) for TNFi (N=309). This study suggested similar rates for RA-ILD as the underlying cause of death (14% [one patient] rituximab-treated vs. 16% [12 patients] TNFi-treated);[1] however, the study was not powered to detect the difference.
- One single-center retrospective cohort study assessed the risk of infection of patients receiving TNFi (alone or in combination with any other antirheumatic drug) (n=59) vs. non-TNFI biologic (rituximab and abatacept) (n=38). The infection rate in the TNFi group vs. non-TNFI biologic group was 1.8 vs. 13.5 per 100 person-year (py), respectively.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 67.

References for Included Studies for PICO 67

1. Druce KL, Iqbal K, Watson KD, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. *RMD open*. 2017;3(1):e000473. doi:https://dx.doi.org/10.1136/rmdopen-2017-000473
2. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clinical rheumatology*. 2016;35(10):2585-9. doi:https://dx.doi.org/10.1007/s10067-016-3357-z

PICO 199: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 200: In rheumatic disease patients with rapidly progressive ILD, what is the impact of abatacept compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 201: In rheumatic disease patients with rapidly progressive ILD, what is the impact of JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 201, we provide indirect evidence from PICO 70 (JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 70.

Key Findings from PICO 70: direct evidence from 1 observational study (Cronin et al., 2021)

- Evidence from one observational study suggested no difference in the respiratory events rate (i.e., composite outcome of hospitalizations and death rate) between patients with a history of JAK inhibitors and rituximab (HR 1.38, [95% CI: 0.36 to 5.28]); however, the sample size and the event rate were very small.
- One observational study found no association between the type of pharmacotherapy and drug discontinuation rate (unadjusted HR 1.90, [95% CI: 0.63 to 5.73]); however, the sample size and the event rate were very small.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 70.

Table 201-1. PICO 133: Excluded Studies

References	Reasons for exclusion
Fan et al., 2022[1]	No comparator of interest

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

References for Included Studies for PICO 70

1. Cronin O, McKnight O, Keir L, Ralston SH, Hirani N, Harris H. A retrospective comparison of respiratory events with JAK inhibitors or rituximab for rheumatoid arthritis in patients with pulmonary disease. *Rheumatology international*. 2021;41(5):921-928. doi:https://dx.doi.org/10.1007/s00296-021-04835-1

PICO 202: In rheumatic disease patients with rapidly progressive ILD, what is the impact of nintedanib compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 113. PICO 202: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 203: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pirfenidone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0--1. PICO 203: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 204: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IVIG compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 205: In rheumatic disease patients with rapidly progressive ILD, what is the impact of oral prednisone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 206: In rheumatic disease patients with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 207: In rheumatic disease patients with rapidly progressive ILD, what is the impact of plasma exchange compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 208: In rheumatic disease patients with rapidly progressive ILD, what is the impact of methotrexate compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0--1. PICO 208: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[1]	Wrong study type

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

PICO 209: In rheumatic disease patients with rapidly progressive ILD, what is the impact of leflunomide compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 210: In rheumatic disease patients with rapidly progressive ILD, what is the impact of cyclophosphamide compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 210: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[1]	Wrong study type
Mao et al., 2020[2]	No intervention of interest

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

2. Mao M-M, Xia S, Guo B-P, et al. Ultra-low dose rituximab as add-on therapy in anti-MDA5-positive patients with polymyositis /dermatomyositis associated ILD. *Respiratory medicine*. 2020;172:105983. doi:https://dx.doi.org/10.1016/j.rmed.2020.105983

PICO 211: In rheumatic disease patients with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Due to the lack of direct evidence for PICO 211, we provide indirect evidence from PICO 80 (calcineurin inhibitors vs azathioprine as first line ILD treatment) below. The certainty of evidence across all critical outcomes was rated Very low for PICO 80.

Key Findings: direct evidence from 2 observational studies

- Kiboshi et al., 2022 found no difference in IMPORTANT outcomes KL-6 levels, %FVC, %DLCO, total GGO score, and total fibrosis score at 12 months follow-up between a very small number (n=18 per group) of individuals in the AZA and TAC groups. The study suggested that the rates of evolution of total fibrosis score, and those corrected by disease duration for 36 months follow-up, were significantly lower in the TAC group than in the AZA group (p=0.17 and 0.25, respectively). However, there was a high dropout rate—39% in the TAC group and 33% in the AZA group.
- Adverse events were reported poorly (CRITICAL outcomes):
  - Only two patients developed an infection in each group.
  - 3 (17%) patients developed mild renal injury at 12 months of follow-up in the TAC group.
  - 2 (11%) developed mild leukopenia in the AZA group.
- Chen et al., 2022 concluded that when comparing tacrolimus with azathioprine, the 12-month survival rate was significantly improved by tacrolimus.

For additional information, please see the Executive Summary, and data provided in Summary of Findings (SOF)/Word tables under PICO 80.

References for Included Studies for PICO 80

1. Kiboshi T, Kotani T, Konma J, et al. Comparison of therapeutic effects of combination therapy with prednisolone and tacrolimus or azathioprine on progressive interstitial pneumonia with systemic sclerosis. *Modern rheumatology*. 2022;32(2):358-364. doi:https://dx.doi.org/10.1080/14397595.2021.1918864
2. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. Frontiers in immunology. 2022;13:978429.

PICO 212: In rheumatic disease patients with rapidly progressive ILD, what is the impact of TNF inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 213: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 214: In rheumatic disease patients with rapidly progressive ILD, what is the impact of abatacept compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 215: In rheumatic disease patients with rapidly progressive ILD, what is the impact of JAK inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 215-1. PICO 215 Excluded Studies

Reference	Reason for exclusion
Fan et al., 2022[1]	No comparator of interest

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 216: In rheumatic disease patients with rapidly progressive ILD, what is the impact of nintedanib compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 216: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 217: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pirfenidone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 217: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 218: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IVIG compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 219: In rheumatic disease patients with rapidly progressive ILD, what is the impact of oral prednisone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 220: In rheumatic disease patients with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 221: In rheumatic disease patients with rapidly progressive ILD, what is the impact of plasma exchange compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 222: In rheumatic disease patients with rapidly progressive ILD, what is the impact of methotrexate compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 222: Excluded Studies

Reference	Reason for exclusion
Tillie-Leblond et al., 2008[1]	Wrong study type

References

1. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: Difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59. doi:https://dx.doi.org/10.1136/thx.2006.069237

PICO 223: In rheumatic disease patients with rapidly progressive ILD, what is the impact of leflunomide compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 224: In rheumatic disease patients with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 225: In rheumatic disease patients with rapidly progressive ILD, what is the impact of TNF inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 226: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 227: In rheumatic disease patients with rapidly progressive ILD, what is the impact of abatacept compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 228: In rheumatic disease patients with rapidly progressive ILD, what is the impact of JAK inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 228-1. PICO 228 Excluded Studies

Reference	Reason for exclusion
Fan et al., 2022[1]	No comparator of interest

References

1. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 229: In rheumatic disease patients with rapidly progressive ILD, what is the impact of nintedanib compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 229: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 230: In rheumatic disease patients with rapidly progressive ILD, what is the impact of pirfenidone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 230: Excluded Studies

Reference	Reason for exclusion
Raghu et al., 2022[1]	Wrong publication type

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2022;205(9):e18-e47. doi:https://dx.doi.org/10.1164/rccm.202202-0399ST

PICO 231: In rheumatic disease patients with rapidly progressive ILD, what is the impact of IVIG compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 232: In rheumatic disease patients with rapidly progressive ILD, what is the impact of oral prednisone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 233: In rheumatic disease patients with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 234: In rheumatic disease patients with rapidly progressive ILD, what is the impact of plasma exchange compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 234-1. PICO 234 Excluded Studies

Reference	Reason for exclusion
Bay et al., 2022[1]	No comparator of interest

References

1. Bay P, e Chambrun MP, Rothstein V, et al. Efficacy of plasma exchange in patients with anti-MDA5 rapidly progressive interstitial lung disease. *Journal of autoimmunity*. 2022;133:102941. doi:https://protect-us.mimecast.com/s/Yx-rCPNY2LiK7mNQhrKs7Q0?domain=dx.doi.org

PICO 235: In rheumatic disease patients with rapidly progressive ILD, what is the impact of dual combination therapy* compared to monotherapy† as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches identified one indirect poor-quality study that addressed this PICO question, comparing a combination of tacrolimus with glucocorticoids to a conventional treatment, represented by either cyclophosphamide (CTX), which was the most frequently used immunosuppressive agent, or methotrexate (MTX) and azathioprine (AZA). This study suggested that tacrolimus was associated with a significantly higher survival rate at 12-month than conventional treatment, tacrolimus was associated with lower relapse rate (38.7% [39/101] vs. 51.6% [81/157], HR 0.55, p=0.003). However, opportunistic infection rate appeared to be higher in the tacrolimus group than in the combination therapy group (66.7% [8/12] vs 45.5% [10/22]), respectively.

Table 235-1. PICO 235: Dual combination therapy vs monotherapy as first line rapidly progressive ILD treatment

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
Chen et al., 2022[1]	Retrospective cohort study	High	A total of 250 patients with idiopathic inflammatory myopathies-associated interstitial lung disease (IIM-ILD)	In retrospective group, GCs was initially administered at 0.8-1.5 mg/kg/day of prednisolone or its equivalent for 4 weeks, thereafter, the existing dose was reduced by 5 mg/day of prednisolone or its equivalent every 4 weeks when the dose was above 20 mg daily. When the daily dosage was below 20mg, the dose was reduced by 2.5 mg/day of prednisolone or its equivalent every 2-4 weeks. The use of GCs should be kept at the lowest possible dose. Oral tacrolimus was given twice daily (0.075 mg/kg of body weight) to achieve a plasma trough level of 5–10 ng/ml	A significant improvement in **12-month survival rate** after adjustment was observed in tacrolimus group compared to conventional treatment group after adjustment (log-rank p =0.0029, weighted HR=0.33; 95% CI: 0.16 to 0.68, P=0.002, n=93) **Relapse events**: 39 patients (38.7%) in tacrolimus group and 81 patients (51.6%) in conventional therapy group. After adjustment, the tacrolimus group showed a significantly lower relapse rate compared with the conventional therapy group (log-rank p=0.0038, weighted HR=0.548, 95% CI: 0.368 to 0.816, P=0.003) **Opportunistic infections** were the most observed adverse events, accounting for 66.7% (8/12) and 45.5% (10/22) of patients in tacrolimus group and combination therapy group.

Ref ID, Author, year	Study type	Risk of Bias	Population Description	Interventions and Comparators	Results
				Retrospective study: Tacrolimus group (n=93), Conventional therapy group (n=157). In the conventional therapy group, cyclophosphamide (CTX) was the most frequently used immunosuppressive agent, followed by methotrexate (MTX) and azathioprine (AZA).	Compared to AZA, the 12-month survival rate was significantly improved by tacrolimus.

Table 0-1. PICO 235 Excluded Studies

Reference	Reason for exclusion
Yang et al., 2021[2]	No intervention of interest
Furuya et al., 2016[3]	No comparator of interest

References

1. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. *Frontiers in immunology*. 2022;13:978429. doi:https://protect-us.mimecast.com/s/Ri1ZCOYZ1KHp6XZ3UrQdkK-?domain=dx.doi.org

2. Yang Q, Li T, Zhang X, et al. Initial predictors for short-term prognosis in anti-melanoma differentiation-associated protein-5 positive patients. *Orphanet Journal of Rare Diseases*. 2021;16(1):58. doi:https://dx.doi.org/10.1186/s13023-021-01705-8

3. Furuya H, Nakajima M, Ikeda K, et al. Prognosis and Treatment of Myositis-Associated Severe Interstitial Lung Disease: A Descriptive Study Using a Nationwide Inpatient Database in Japan. *Arthritis care & research*. 2022;74(3):478-483. doi:https://dx.doi.org/10.1002/acr.24646

* Dual combination therapy examples: oral prednisone/intravenous methylprednisolone and mycophenolate, or oral prednisone/intravenous methylprednisolone and azathioprine, or oral prednisone/intravenous methylprednisolone and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and rituximab, or oral prednisone/intravenous methylprednisolone and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and a JAK inhibitor

† Monotherapy examples: oral prednisone/intravenous methylprednisolone, or mycophenolate, or azathioprine, or a calcineurin inhibitor, or rituximab, or cyclophosphamide

PICO 236: In rheumatic disease patients with rapidly progressive ILD, what is the impact of triple combination therapy‡ compared to monotherapy† as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Low**

Key Findings:

- Triple therapy (high-dose GCs, TAC, and IV CYC) showed significantly higher 6-month survival rates compared with step-up treatment (high-dose GCs with stepwise addition of immunosuppressants.
- Cytomegalovirus reactivation occurred more frequently in the combination therapy group compared to the step-up group (85% vs 33%).

Summary: We identified one study that addressed this PICO (Tsuji et al. 2020[1]). This study enrolled a total of 29 patients with new onset MDA-5 positive DM-ILD. Patients were prospectively treated with combined high-dose glucocorticoids (GCs), tacrolimus (TAC), and IV cyclophosphamide (CYC), and were compared to a historical control group (n=15) who received "step-up" treatment with high-dose GCs and stepwise addition of immunosuppressants. Plasmapheresis was used if a patient's condition worsened after the regimen started. The primary endpoint was 6-month survival, and the secondary endpoints were a 12-month survival rate, adverse events, and changes in laboratory data.

The combined immunosuppressive regimen group showed significantly higher 6-month survival rates than the step-up treatment group (89% versus 33%; $P < 0.0001$). Over a period of 52 weeks, improvements in anti–MDA-5 titers, serum ferritin levels, vital capacity, and chest high-resolution computed tomography scores were observed. The combined immunosuppressive regimen group received IV CYC nearly 20 days earlier with shorter intervals and tended to receive plasmapheresis more often than patients undergoing step-up treatment. Cytomegalovirus reactivation occurred more frequently in the Triple therapy group compared to the step-up group (85% vs 33%.)

Reference	Study design	Risk of bias	Outcomes	Patients	Treatment	Results
Tsuji et al. 2020[1]	Prospective cohort study	High	Primary endpoint: 6-month survival rate Secondary endpoint: 12-month survival rate, adverse events, changes in lab data	Adult Japanese patients with new-onset MDA-5-positive DM-ILD (*n*=29) treated with combined high-dose GCs, tac, IV CYC, and possible PLEX vs. historical controls (*n*=15) who received "step-up" treatment (high-dose GCs and stepwise addition of immunosuppressant) Additional historical control group who received combined high-dose GCs, CsA, IV CYC also compared to more recent prospective cohort	Prednisolone 1 mg/kg/day (4 weeks), then gradually reduced + IV CYC (500-1,000 mg/m^2 every 2 weeks for 6 doses, then every 4-8 weeks for total 10-15 infusions)+tac (goal trough 10-12 ng/ml); PLEX could be initiated if condition worsened (performed 1-3 times per week for 3-13 consecutive weeks)	Triple therapy group had higher 6-month mortality than step-up group (89% vs. 33%, p<0.0001) Improvements in anti-MDA-5 titers, serum ferritin levels, FVC and HRCT scores also noted over 52-week period in Triple therapy group. **Adverse events summarized in Table 30-3** **Most prevalent AE was infection:** Overall: 23 (85%), 12 (80%) Bacterial infection: 10 (37), 5 (33) CMV: 23 (85%), 5 (33%) HSV/VZV: 2 (7) 2 (13) Candidiasis :15 (56) 5 (33) Aspergillus: 2 (7) 0 (0) PCP: 3 (11) 2 (13) Other fungal infections: 1 (4) 2 (13) PLEX initiation occurred in 31% of combined IS group and 7% of step-up group (NS)

Table 0-1. PICO 236 Excluded Studies

Reference	Reason for exclusion
Furuya et al., 2016[2]	No comparator of interest
Chen et al., 2022[3]	No comparator of interest

References

1. Tsuji H, Nakashima R, Hosono Y, et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases

Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. Arthritis & rheumatology (Hoboken, NJ). 2020;72(3):488-498. doi:https://dx.doi.org/10.1002/art.41105

2. Furuya H, Nakajima M, Ikeda K, et al. Prognosis and Treatment of Myositis-Associated Severe Interstitial Lung Disease: A Descriptive Study Using a Nationwide Inpatient Database in Japan. *Arthritis care & research*. 2022;74(3):478-483. doi:https://dx.doi.org/10.1002/acr.24646

3. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. *Frontiers in immunology*. 2022;13:978429. doi:https://protect-us.mimecast.com/s/Ri1ZCOYZ1KHp6XZ3UrQdkK-?domain=dx.doi.org

PICO 237: In rheumatic disease patients with rapidly progressive ILD, what is the impact of triple combination therapy‡ compared to dual combination therapy* as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

Table 0-1. PICO 237 Excluded Studies

Reference	Reason for exclusion
Vuillard et al., 2018[1]	No outcomes of interest
Fan et al., 2022[2]	No comparator of interest

References

1. Vuillard C, Pineton de Chambrun M, e Prost N, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. *Annals of Intensive Care*. 2018;8(1):87. doi:https://dx.doi.org/10.1186/s13613-018-0433-3

2. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 238: In rheumatic disease patients with rapidly progressive ILD, what is the impact of using IVIG and/or plasma exchange in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ compared to using monotherapy†, dual combination therapy*, or triple combination therapy‡ alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings:

- All-cause mortality
  - Evidence from one retrospective observational study (Wang et al., 2021[1]) suggested a lower all-cause mortality rate at 3 months (IVIG 6 [19.4%]; non-IVIG 9 [52.9%], p=0.016) and 6 months of follow-up (IVIG 7 [22.6%]; non-IVIG 9 [52.9%], p=0.033) in the IVIG group vs. among those without IVIG history (very low quality of evidence).
  - Evidence from one retrospective observational study (Shirakashi et al., 2020[2] suggested a protective effect of plasma exchange for the 3-year cumulative survival rate, compared to individuals without PE (5/8 (62.5%) vs. 0/5 (0%).
  - Evidence from one retrospective observational study (Bay et al., 2022[3]) suggested one-year transplant-free survival rates could be higher in PLEX-compared to PLEX + patients (p = 0.05).
- Evidence from one retrospective observational study suggested a similar infection rate at both 3- and 6-months (IVIG 8 [25.8%]; non-IVIG 3 [17.6%], p=0.776) of follow-up.

Summary: We included three poor-quality retrospective observational studies that addressed this PICO question. Wang et al.[1] assessed outcomes in 48 patients from China with new onset of RP-ILD secondary to MDA5 dermatomyositis between 2018 and 2020. Thirty-one patients had a history of IVIG (mean age 51.9, 61% female) as initial therapy in addition to standard-of-care immunosuppression; 17 patients received standard-of-care alone (mean age 49.9, 58.8% female). Patients in the IVIG group had initiated treatment at week one of their diagnosis (400 mg/kg/day for 5 days in the first course) and had additional IVIG courses within 2–4 weeks. There were no statistically significant differences in MDA5 titers, presence of Ro52 antibodies, baseline oxygen saturation levels, or baseline CT findings. The IVIG group demonstrated a lower 3-month (p=0.016) and 6-month (p=0.033) all-cause mortality rate; however, the event rate was very small. The study found a higher remission rate (i.e., relieved respiratory symptom and halted progression or reduction of ILD on HRCT) in the IVIG patients compared to those without IVIG at 3 months of follow-up (IVIG 71.0% vs. no IVIG 41.2%, p=0.044). However, there was no difference in the remission rate between the groups at 6 months of follow-up (p=0.241). There was no statistically significant difference in glucocorticoid dosages at six months or infection rates

between the two groups. This study does not allow attributing mortality and remission benefits to the IVIG therapy due to selective bias (i.e., individuals with IVIG therapy likely had a lower baseline mortality risk than those in the non-IVIG group).

Shirakashi et al., 2022[2] assessed 13 anti-MDA5 positive RP-ILD patients who progressed despite standard immunosuppressive therapy with high-dose steroids, a calcineurin inhibitor, and IV cyclophosphamide. The 3-year cumulative survival rate for the patients who received plasma exchange was 5/8 (62.5%) vs. 0/5 (0%) in those without plasma exchange.[2] However, the number of participants was very small to conclude the PE protective effect.

Bay et al., 2022[3] performed a retrospective study across 18 centers in France that included 51 patients with MDA5-positive RP-ILD. 25 (49% of these patients received PLEX in addition to standard immunosuppression). The rate of one-year transplant-free survival in the PLEX+ vs. PLEX- group was 20% vs. 54%, respectively (p = 0.05). The number of participants and events was very small.

Table 238-1: PICO 238. Evidence of the impact of using IVIG and/or plasma exchange in addition to monotherapy†, dual combination therapy*, or triple combination therapy vs. monotherapy†, dual combination therapy*, or triple combination therapy alone

Author, year	Study type	Risk of Bias	Population Description	Outcomes	Results	GRADE Certainty Rating
Wang et al., 2022[1]	Retrospective observational study	High	**Age:** ~50 years old, mean **% female:** ~60% 48 patients (China) with new onset of RP-ILD secondary to MDA5 DM. 31 patients had a history of IVIG (400 mg/kg/day for 5 consecutive days in the first course, and additional courses were applied 2–4 weeks later) 17 patients had no history of IVIG	Follow-up: 3 and 6 months ● All-cause mortality (Critical) ● Infection rate (Critical) ● Remission rate (Important)	**All-cause mortality** *3 months of follow-up* IVIG: 6 (19.4%) no IVIG: 9 (52.9%) p=0.016 *6 months of follow-up* IVIG: 7 (22.6%) no IVIG: 9 (52.9%) p=0.033 **Infection rate** *3 months of follow-up* IVIG: 8 (25.8%) no IVIG: 3 (17.6%) p=0.776	**Very low**

Author, year	Study type	Risk of Bias	Population Description	Outcomes	Results	GRADE Certainty Rating
					6 months of follow-up IVIG: 8 (25.8%) no IVIG: 3 (17.6%) p=0.776 **Remission rate** *3 months of follow-up* IVIG: 22 (71.0%) no IVIG: 7 (41.2%) p=0.044 *6 months of follow-up* IVIG: 20 (64.5%) no IVIG: 8 (47.1%) p=0.241	
Shirakashi et al., 2020[2]	Retrospective observational study	High	**Age:** 39.5 to 67.5 years old, range **% female:** ~65% 38 anti-MDA5-positive DM-ILD patients who received the combined immunosuppressive therapy were retrospectively reviewed. Their serum cytokines were evaluated by multiplex assay before treatment. The patients were divided into two groups: those who achieved remission without exacerbation of respiratory dysfunction (n=25, group A) and those who progressed to hypoxemia during the treatment (n=13, group B).	Follow-up: 3 years ● All-cause mortality (Critical)	**All-cause mortality** The 3-year cumulative survival rate for the patients who received plasma exchange was 5/8 (62.5%) vs. 0/5 (0%) in those without plasma exchange	**Very low**

Author, year	Study type	Risk of Bias	Population Description	Outcomes	Results	GRADE Certainty Rating
Bay et al., 2022[3]	Retrospective observational study	High	**Age:** 51 years old, mean **% female:** ~67% This French nationwide multicenter retrospective study included all (n=51) MDA5-DM RP-ILD patients from 2012 to 2021 admitted to 18 centers. The primary endpoint was one-year transplant-free survival.	Follow-up: 1 year ● One-year transplant-free survival (Critical)	**One-year transplant-free survival** PLEX + vs. PLEX-were 20% vs. 54% (p = 0.01), respectively. The Kaplan–Meier estimated probabilities of one-year transplant-free survival was statistically higher in PLEX-compared to PLEX + patients (p = 0.05).	**Very low**

† Monotherapy examples: oral prednisone/intravenous methylprednisolone, or mycophenolate, or azathioprine, or a calcineurin inhibitor, or rituximab, or cyclophosphamide

* Dual combination therapy examples: oral prednisone/intravenous methylprednisolone and mycophenolate, or oral prednisone/intravenous methylprednisolone and azathioprine, or oral prednisone/intravenous methylprednisolone and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and rituximab, or oral prednisone/intravenous methylprednisolone and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and a JAK inhibitor

‡ Triple combination therapy examples: oral prednisone/intravenous methylprednisolone and rituximab and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and cyclophosphamide and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and mycophenolate and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and mycophenolate and abatacept, or oral prednisone/intravenous methylprednisolone and rituximab and mycophenolate

Table 238-2. PICO 238 Excluded Studies

Reference	Reason for exclusion
Vuillard et al., 2018[4]	No outcomes of interest
Furuya et al., 2022[5]	No outcomes of interest
Fan et al., 2022[6]	No intervention of interest

References

1. Wang LM, Yang QH, Zhang L, et al. Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Rheumatology (Oxford, England)*. 2021;doi:https://dx.doi.org/10.1093/rheumatology/keab928

2. Shirakashi M, Nakashima R, Tsuji H, et al. Efficacy of plasma exchange in anti-MDA5-positive dermatomyositis with interstitial lung disease under combined immunosuppressive treatment. *Rheumatology (Oxford, England)*. 2020;59(11):3284-3292. doi:https://dx.doi.org/10.1093/rheumatology/keaa123

3. Bay P, e Chambrun MP, Rothstein V, et al. Efficacy of plasma exchange in patients with anti-MDA5 rapidly progressive interstitial lung disease. *Journal of autoimmunity*. 2022;133:102941. doi:https://protect-us.mimecast.com/s/Yx-rCPNY2LiK7mNQhrKs7Q0?domain=dx.doi.org

4. Vuillard C, Pineton de Chambrun M, e Prost N, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. *Annals of Intensive Care*. 2018;8(1):87. doi:https://dx.doi.org/10.1186/s13613-018-0433-3

5. Furuya H, Nakajima M, Ikeda K, et al. Prognosis and Treatment of Myositis-Associated Severe Interstitial Lung Disease: A Descriptive Study Using a Nationwide Inpatient Database in Japan. *Arthritis care & research*. 2022;74(3):478-483. doi:https://dx.doi.org/10.1002/acr.24646

6. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 239: In rheumatic disease patients with rapidly progressive ILD, what is the impact of using an antifibrotic (e.g., nintedanib or pirfenidone) in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ compared to using monotherapy†, dual combination therapy*, or triple combination therapy‡ alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Key Findings: Very low certainty of evidence suggests that add-on pirfenidone provides no benefit to patients who receive conventional treatment (high-dose prednisolone and/or immunosuppressants [cyclosporine, mycophenolate, azathioprine, cyclophosphamide]) at 6 months of follow-up. Adverse events were reported poorly which does not allow a conclusion about the safety profile.

Summary: We included one poor-quality retrospective study of individuals (China) diagnosed with clinically amyopathic dermatomyositis (CADM) RP-ILD with a disease duration <6 months. The individuals in the intervention group received pirfenidone (1800 mg/d) and conventional treatment (high-dose prednisolone and/or immunosuppressants [cyclosporine, mycophenolate, azathioprine, cyclophosphamide]). Patients in the control group had no history of pirfenidone and received conventional therapy only.

This study provided very low certainty of evidence that add-on pirfenidone provides no benefit to patients who receive conventional treatment (high-dose prednisolone and/or immunosuppressants [cyclosporine, mycophenolate, azathioprine, cyclophosphamide]) at 6 months of follow-up. Adverse events were reported poorly which does not allow a conclusion about the safety profile.

Table 239-1: PICO 239 Antifibrotics (e.g., nintedanib or pirfenidone) in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ compared to using monotherapy†, dual combination therapy*, or triple combination therapy‡ alone

Author, Year	Study	Risk of Bias	Follow-up	Population Description	Treatment and Comparator	Results
Li et al., 2016[1]	Retrospective study	High	Up to 6 months	**Age**: 46.3 (11.3) years in the intervention (n=30) and 51.8 (7.8) years in the control (n=27) group **% female**: ~70%	**Intervention**: Pirfenidone (1800 mg/d) + conventional treatment (high-dose prednisolone and/or immunosuppressants [cyclosporine,	**Mortality** (Critical Outcome) <u>Rate:</u> Intervention (n=30): 51.9% Control (n=27): 36.7% p=0.223 *No difference*

				Duration of CADM (months): 3.2 months and 2.9 months in the intervention and control groups, respectively Patients diagnosed with clinically amyopathic dermatomyositis (CADM) RP-ILD with a disease duration <6 months at Renji Hospital South Campus (China) from June 2014 to November 2015.	mycophenolate, azathioprine, cyclophosphamide]) **Control**: Conventional treatment (high-dose prednisolone and/or immunosuppressants [cyclosporine, mycophenolate, azathioprine, cyclophosphamide])	<u>Survival of acute ILD patients (disease duration <3 months)</u> Intervention (n=20): 50.0% Control (n=18): 50.0% p=0.386 *No difference* <u>Survival of subacute ILD patients (disease duration 3-6 months)</u> Intervention (n=10): 90% Control (n=9): 44.4% p=0.045 *Borderline no difference* **Adverse Events** (Critical Outcome) The elevations of hepatic enzyme (30%) and gastrointestinal reaction (13.3%) were common, but most of these events were mild to moderate in severity and were reversible. Three adverse events (10%) led to treatment discontinuation in 3 survivors (2 patients with acute ILD and 1 patient with subacute ILD) and were elevated hepatic enzyme levels, rash and diarrhea.

† Monotherapy examples: oral prednisone/intravenous methylprednisolone, or mycophenolate, or azathioprine, or a calcineurin inhibitor, or rituximab, or cyclophosphamide

* Dual combination therapy examples: oral prednisone/intravenous methylprednisolone and mycophenolate, or oral prednisone/intravenous methylprednisolone and azathioprine, or oral prednisone/intravenous methylprednisolone and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and rituximab, or oral prednisone/intravenous methylprednisolone and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and a JAK inhibitor

‡ Triple combination therapy examples: oral prednisone/intravenous methylprednisolone and rituximab and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and cyclophosphamide and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and mycophenolate and a calcineurin inhibitor, or oral prednisone/intravenous

methylprednisolone and mycophenolate and abatacept, or oral prednisone/intravenous methylprednisolone and rituximab and mycophenolate

Table 0-1. PICO 239 Excluded Studies

Reference	Reason for exclusion
Furuya et al., 2016[2]	No outcomes of interest
Chen et al., 2022[3]	No comparator of interest
Fan et al. 2022[4]	No intervention of interest

References

1. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Scientific reports*. 2016;6:33226. doi:https://dx.doi.org/10.1038/srep33226

2. Furuya H, Nakajima M, Ikeda K, et al. Prognosis and Treatment of Myositis-Associated Severe Interstitial Lung Disease: A Descriptive Study Using a Nationwide Inpatient Database in Japan. *Arthritis care & research*. 2022;74(3):478-483. doi:https://dx.doi.org/10.1002/acr.24646

3. Chen Y, Bai Z, Zhang Z, Hu Q, Zhong J, Dong L. The efficacy and safety of tacrolimus on top of glucocorticoids in the management of IIM-ILD: A retrospective and prospective study. *Frontiers in immunology*. 2022;13:978429. doi:https://protect-us.mimecast.com/s/Ri1ZCOYZ1KHp6XZ3UrQdkK-?domain=dx.doi.org

4. Fan L, Lyu W, Liu H, et al. A Retrospective Analysis of Outcome in Melanoma Differentiation-Associated Gene 5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus. *The Journal of rheumatology*. 2022;49(12):1356-1364. doi:https://protect-us.mimecast.com/s/t_w8C0R9lKHGRWgjcLlPVFy?domain=dx.doi.org

PICO 240: In rheumatic disease patients with rapidly progressive ILD, what is the impact of referral for stem cell transplant compared to optimal medical management as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.

PICO 241: In rheumatic disease patients with rapidly progressive ILD, what is the impact of referral for lung transplant compared to optimal medical management as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Certainty of evidence across all critical outcomes: **Very low**

Summary: The literature searches did not identify any studies that addressed this PICO question.