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2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

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Objective. We provide evidence-based recommendations regarding the treatment of interstitial lung disease (ILD) in adults with systemic autoimmune rheumatic diseases (SARDs).

Methods. We developed clinically relevant population, intervention, comparator, and outcomes questions. A systematic literature review was then performed, and the available evidence was rated using the Grading of Recommendations, Assessment, Development, and Evaluation methodology. A panel of clinicians and patients reached consensus on the direction and strength of the recommendations.

Results. Thirty-five recommendations were generated (including two strong recommendations) for first-line SARD-ILD treatment, treatment of SARD-ILD progression despite first-line ILD therapy, and treatment of rapidly progressive ILD. The strong recommendations were against using glucocorticoids in systemic sclerosis–ILD as a first-line ILD

therapy and after ILD progression. Otherwise, glucocorticoids are conditionally recommended for first-line ILD treatment in all other SARDs.

Conclusion. This clinical practice guideline presents the first recommendations endorsed by the American College of Rheumatology and American College of Chest Physicians for the treatment of ILD in people with SARDs.

INTRODUCTION

Interstitial lung disease (ILD) is a significant cause of morbidity and mortality in people with systemic autoimmune rheumatic diseases (SARDs). The American College of Rheumatology (ACR) has developed guidelines for screening those at risk for ILD and for the monitoring and treatment of those who have developed SARD-ILD, reported separately.[1] This guideline provides recommendations for the treatment of ILD in adults with those SARDs at greatest ILD risk, including systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM including polymyositis, dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy), mixed connective tissue disease (MCTD), and Sjögren disease (SjD).[2,3]

METHODS

We followed the ACR guideline development process and policy for managing conflicts of interest and disclosures (https://rheumatology.org/clinical-practice-guidelines), including Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.[4–6] Supplementary Materials 1 describes our methods. The core leadership team (including rheumatologists, methodologists, a pulmonologist, and a radiologist) drafted clinical population, intervention, comparator, and outcomes (PICO) questions (Supplementary Materials 2). The Literature Review Team conducted a systematic literature review, rated the quality of evidence (high, moderate, low, or very low), and produced the evidence report (Supplementary Materials 3). A Patient Panel was convened that included 21 people with SARDs (SSc n = 7, RA n = 5, IIM n = 7, MCTD n = 3, SjD n = 8, with some patients having more than one diagnosis) at risk for (n = 4 [19%]) or diagnosed with ILD (n = 17 [81%]); the median age was 53 years (range 33–73 years), and the panel included n = 16 women (71%), with n = 14 White individuals (67%), n = 7 Black or multiracial individuals (33%), and n = 2 Hispanic individuals (10%). They met virtually with three members of the Core Team (MBB, MDG, and RDM) and two ACR staff, providing their values and preferences related to ILD screening, monitoring, and treatment.[7] An expert Voting Panel including rheumatologists (n = 19), pulmonologists (n = 4), a radiologist (n = 1), and Patient Panel representatives (n = 3) reviewed the evidence report and formulated and voted on the recommendations at virtual meetings (February to March 2023).

Consensus required ≥70% agreement on both direction and strength (strong or conditional) to make a recommendation.

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Strong recommendations indicate confidence that benefits of an intervention clearly outweigh the harms (or vice versa); conditional recommendations denote uncertainty regarding net benefit. The Panel voted on paired comparisons of treatment options resulting in a hierarchy of preferred treatments. Because of limitations in evidence and factors that might affect choices for specific patients (eg, extrapulmonary manifestations, provider comfort with medications and monitoring requirements, costs, access), we do not emphasize a mandatory treatment sequence but instead provide a range of "preferred" or "additional" ILD treatment options. Supplementary Materials 4 provides rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel.

Scope

Patients. This guideline applies only to adults with SSc, RA, MCTD, IIMs, and SjD-associated ILD, but not individuals who are pregnant or nursing.

Interventions. This guideline addresses methotrexate, leflunomide, azathioprine, cyclophosphamide, mycophenolate, calcineurin inhibitors (CNIs; tacrolimus, cyclosporine), tumor necrosis factor inhibitors (TNFi; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), tocilizumab, rituximab, abatacept, JAK inhibitors (JAKi; tofacitinib, baricitinib, upadacitinib), antifibrotic agents (pirfenidone; nintedanib), glucocorticoids (oral prednisone, intravenous methylprednisolone), intravenous immunoglobulin (IVIG), plasma exchange, and referrals for stem cell and lung transplantation.

Outcomes. Critical outcomes included death, disability, quality of life (QoL), and adverse events, including 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, and change in extent of ILD or ILD progression on high-resolution computed tomography of the chest (HRCT chest).

Progression of ILD. Progression (as an outcome) was defined using the INBUILD trial criteria,[8] ie, decline in FVC of ≥10% the predicted value, decline in FVC of 5% to <10% the predicted value and worsening of respiratory symptoms or increased fibrosis on HRCT chest, or worsening of respiratory symptoms and increased fibrosis all within 24 months. These criteria may be useful in assessments for disease progression but are not requisite for routine follow-up and clinical decision-making by practitioners and patients.

Rapidly progressive ILD. Rapidly progressive ILD (RP-ILD) represents a subpopulation of ILD characterized by rapid progression from breathing room air or a patient's baseline oxygen requirement to a high oxygen requirement or intubation within days to weeks without a documented alternative cause (eg, infection, heart failure), which can be seen in a diagnosis of acute interstitial pneumonia.[9,10] Progressive pulmonary fibrosis (PPF) and progressive fibrosing ILD (PF-ILD) differ from RP-ILD, and these terms are not interchangeable.[11]

Recommendations related to RP-ILD were considered for monotherapy, dual therapy, and triple therapy. Monotherapy agents considered were oral/intravenous glucocorticoids, mycophenolate, azathioprine, CNI, rituximab, and cyclophosphamide. Dual combination therapy was defined as simultaneous use of glucocorticoids and one of the above therapies. Triple combination therapy was defined as simultaneous use of glucocorticoids and two of the above therapies.[12]

RESULTS/RECOMMENDATIONS

Thirty-five treatment recommendations (Table 1, Figures 1, 2, and 3) are based on 216 PICO questions. The literature search identified 5,235 records (including screening, monitoring, and treatment). After excluding 4,038 titles and abstracts, 1,197 full-text articles were reviewed, 1,083 excluded, and 117 included: screening (n = 10), monitoring (n = 17), and treatment (n = 90) (Supplementary Material 5 and 6). Table 2 summarizes Voting Panel decisions, PICO questions, certainty of evidence, and evidence that led to treatment recommendations. Table 3 provides guidance on medication toxicity and monitoring. Table 4 summarizes integrative and pharmacologic interventions beyond the scope of this guideline.

Recommendations for management of SARD-ILD: first-line ILD treatment

Certainty of all evidence was low to very low (Table 2) (Supplementary Material 3). Although PICOs included head-to-head comparisons of treatments to create a hierarchy, limited evidence on the differences among individual therapies led to grouping first-line ILD treatment options into "preferred" therapies (expected to be most prescribed) and "additional options" (may be appropriate in certain situations) (Figure 1).

For people with SARD-ILD other than SSc-ILD, we conditionally recommend glucocorticoids as a first-line ILD treatment.

Because glucocorticoids are generally used in combination with other immunosuppressive agents and there is value in short-term glucocorticoid exposure, they are presented separately from other immunosuppressives. Oral prednisone is commonly used in SARD-ILD other than SSc-ILD, and intravenous pulse methylprednisolone is typically reserved for acute onset or severe ILD.[24,25] Glucocorticoids might not be used in people with predominantly fibrotic disease (eg, RA with a usual interstitial

Table 1. Summary of recommendations for management of SARD-ILD*

Recommendations for management of SARD-ILD: first ILD treatment
For people with SARD-ILD other than SSc-ILD, we **conditionally** recommend glucocorticoids as a first-line ILD treatment.
For people with SSc-ILD, we **strongly** recommend *against* glucocorticoids as a first-line ILD treatment.
For people with SARD-ILD, we **conditionally** recommend mycophenolate, azathioprine, rituximab, and cyclophosphamide as first-line ILD treatment options.
For people with SSc-ILD and MCTD-ILD, we **conditionally** recommend tocilizumab as a first-line ILD treatment option.
For people with SARD-ILD, we **conditionally** recommend *against* leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.
For people with SSc-ILD, we **conditionally** recommend nintedanib as a first-line ILD treatment option.
For people with SjD-ILD, IIM-ILD, and MCTD-ILD, we **conditionally** recommend *against* nintedanib as a first-line ILD treatment option.
For people with RA-ILD, the Panel was not able to come to consensus on whether to recommend nintedanib as a first-line ILD treatment option.
For people with SARD-ILD, we **conditionally** recommend *against* pirfenidone as a first-line ILD treatment option.
For people with SARD-ILD receiving mycophenolate without evidence of ILD progression, we **conditionally** recommend *against* adding nintedanib or pirfenidone to mycophenolate.
For people with SARD-ILD, we **conditionally** recommend *against* upfront combination of nintedanib or pirfenidone with mycophenolate over mycophenolate alone as first-line ILD treatment options.
For people with IIM-ILD, we **conditionally** recommend JAKi as a first-line ILD treatment option.
For people with SARD-ILD other than IIM-ILD, we **conditionally** recommend *against* JAKi as a first-line ILD treatment option.
For people with IIM-ILD, we **conditionally** recommend CNIs as a first-line ILD treatment option.
For people with SARD-ILD other than IIM-ILD, we **conditionally** recommend *against* CNIs as a first-line ILD treatment option.
For people with SARD-ILD, we **conditionally** recommend *against* IVIG or plasma exchange as first-line ILD treatment options.
For people with SARD-associated ILD, we **conditionally** recommend optimal medical management over referral for stem cell or lung transplantation as first-line ILD treatment options.
Recommendations for management of SARD-ILD progression despite first-line ILD treatment
For people with SSc-ILD progression despite first ILD treatment, we **strongly** recommend *against* using long-term glucocorticoids, and in other SARD-ILD, we conditionally recommend *against* using long-term glucocorticoids.
For people with SARD-ILD progression despite first ILD treatment, we **conditionally** recommend mycophenolate, rituximab, cyclophosphamide, and nintedanib as treatment options.
For people with RA-ILD progression despite first ILD treatment, we **conditionally** recommend adding pirfenidone as a treatment option.
For people with SARD-ILD other than RA-ILD progression despite first ILD treatment, we **conditionally** recommend *against* adding pirfenidone as a treatment option.
For people with SSc-ILD, MCTD-ILD, or RA-ILD progression despite first ILD treatment, we **conditionally** recommend using tocilizumab as a treatment option.
For people with SjD-ILD and IIM-ILD progression despite first ILD treatment, we **conditionally** recommend *against* using tocilizumab as a treatment option.
For people with IIM-ILD progression despite first ILD treatments, we **conditionally** recommend using a CNI as a treatment option.
For people with SARD-ILD other than IIM-ILD progression despite first ILD treatments, we **conditionally** recommend *against* using a CNI as a treatment option.
For people with IIM-ILD progression despite first ILD treatment, we **conditionally** recommend using JAKi as a treatment option.
For people with IIM-ILD and MCTD-ILD progression despite first ILD treatment, we **conditionally** recommend adding IVIG as a treatment option.
For people with SARD-ILD progression despite first ILD treatment, we **conditionally** recommend *against* using plasma exchange as a treatment option.
For people with SSc-ILD progression despite first ILD treatment, we **conditionally** recommend referral for stem cell transplantation and/or lung transplantation.
Recommendations for management of SARD with RP-ILD
For people with SARD and RP-ILD, we **conditionally** recommend pulse intravenous methylprednisolone as a first-line RP-ILD treatment.
For people with SARD and RP-ILD, we **conditionally** recommend rituximab, cyclophosphamide, IVIG, mycophenolate, CNI, and JAKi as first-line RP-ILD treatment options.
For people with SARD and RP-ILD, we **conditionally** recommend *against* methotrexate, leflunomide, azathioprine, TNFi, abatacept, tocilizumab, nintedanib, pirfenidone, and plasma exchange as first-line RP-ILD treatment options.
For people with RP-ILD, we **conditionally** recommend upfront combination therapy (triple therapy for those with confirmed or suspected MDA-5 and double or triple therapy for those without confirmed or suspected MDA-5) over monotherapy as first-line treatment.
For people with SARD and RP-ILD, we **conditionally** recommend *against* referral for stem cell transplantation over optimal medical management as a first-line RP-ILD treatment.
For people with SARD and RP-ILD, we **conditionally** recommend early referral for lung transplantation over later referral after progression on optimal medical management.

* CNI, calcineurin inhibitor; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; JAKi, JAK inhibitor; MCTD, mixed connective tissue disease; MDA-5, melanoma differentiation-associated protein 5; RA, rheumatoid arthritis; RP, rapidly progressive; SARD, systemic autoimmune rheumatic disease; SjD, Sjögren disease; SSc, systemic sclerosis; TNFi, tumor necrosis factor inhibitor.

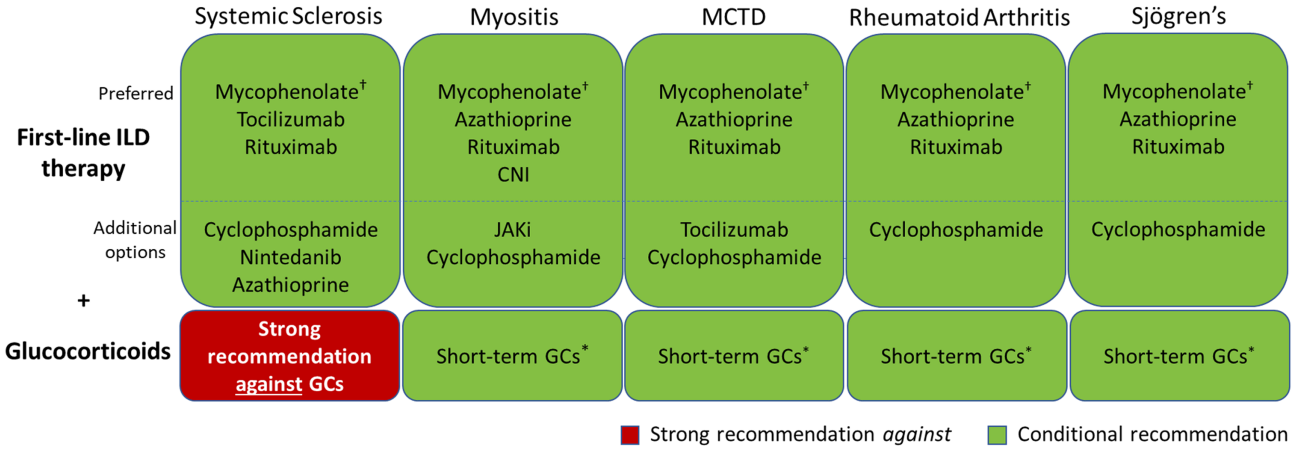

Figure 1. Initial treatment options for the treatment of ILD associated with systemic autoimmune rheumatic diseases of interest. * Decisions on GC dose and use of oral versus intravenous therapy depend on severity of disease. GCs should be used cautiously in patients with MCTD with an SSc phenotype who may be at increased risk of renal crisis. Short-term is defined as 3 months or less. † Treatments are listed in order based on a hierarchy established by head-to-head votes, although the panel noted that decisions on which first-line therapy to use were dependent on specific situations and patient factors. In all diseases, mycophenolate was conditionally recommended over the other listed therapies. Therapies are divided into "preferred" and "additional" options based on the rank-order hierarchy. CNI, calcineurin inhibitor; GC, glucocorticoid; ILD, interstitial lung disease; JAKi, JAK inhibitor; MCTD, mixed connective tissue disease; SSc, systemic sclerosis.

pneumonia [UIP] pattern), but not all panelists agreed. Glucocorticoids should be used with caution in people with MCTD-ILD with SSc features or IIM-ILD with SSc antibodies given the risk for scleroderma renal crisis (SRC).[26–29]

For people with SSc-ILD, we strongly recommend *against* glucocorticoids as first-line ILD treatment.

Glucocorticoids have been associated with SRC, particularly in doses of prednisone (or its equivalent) >15 mg daily, although

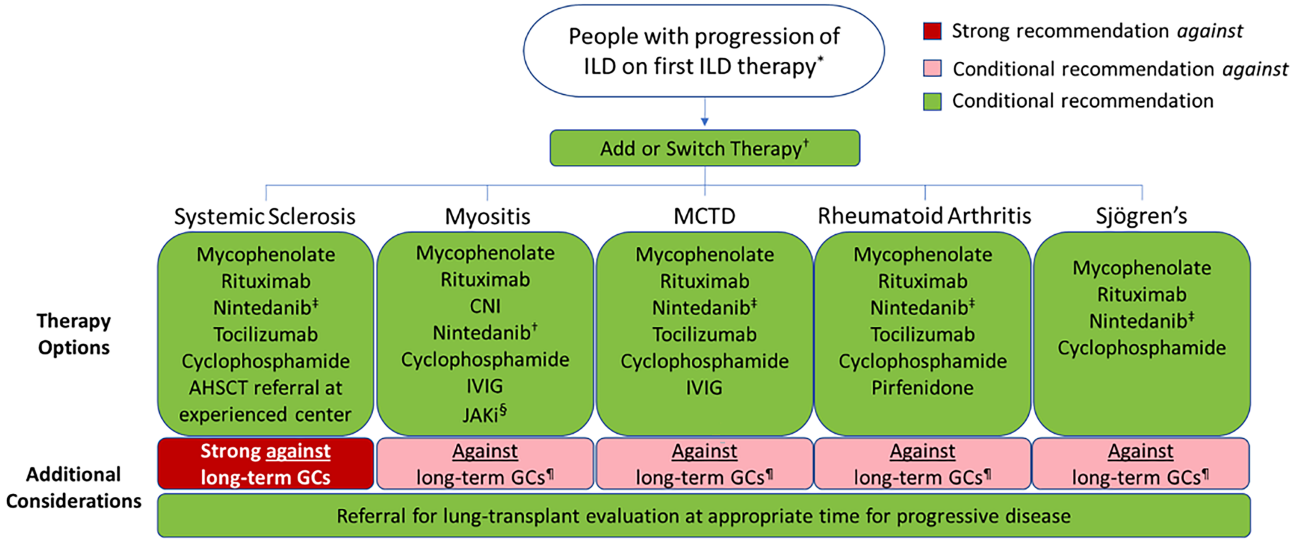

Figure 2. Management of SARD-ILD with progression of ILD despite first ILD therapy. * If intolerance leads to suboptimal dosing of first-line therapy, consider switching to an alternative first-line therapy. † Therapies are generally listed in order based on a hierarchy established by head-to-head votes, but decisions depend on specific clinical situations. Decision on whether to switch therapy or add to current therapy depends on current therapy and on which therapy is being initiated. Cyclophosphamide is not typically used in combination with other therapies, whereas others may be used individually or in combination. ‡ Decision on use of nintedanib vs immunosuppression depends on pace of progression and amount of fibrotic disease or presence of a usual interstitial pneumonia pattern on CT chest. § JAKi conditionally recommended as an option particularly in patients with anti–MDA-5. ¶ Short-term glucocorticoids may be of use in some patients with disease flares or as a bridge when switching therapy. AHSCT, autologous hematopoietic stem cell transplantation; CNI, calcineurin inhibitor; CT, computed tomography; GC, glucocorticoid; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; JAKi, JAK inhibitor; MCTD, mixed connective tissue disease; MDA-5, melanoma differentiation-associated protein 5; SARD, systemic autoimmune rheumatic disease.

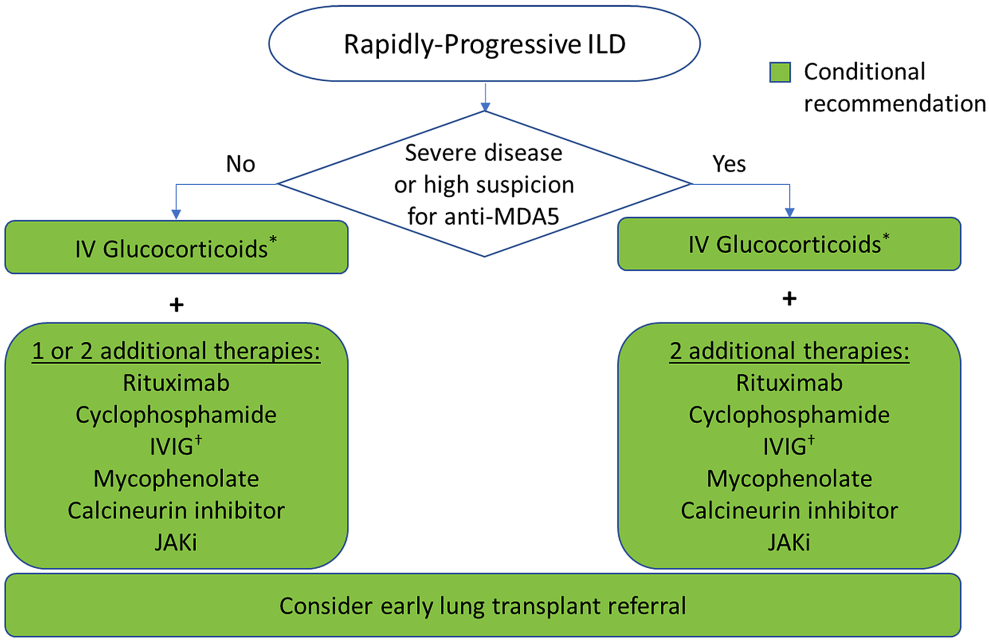

Figure 3. Management of SARD with rapidly progressive ILD. * In rare patients with systemic sclerosis with rapidly progressive ILD, there was no consensus on whether or not to use glucocorticoids; if used, patients should be monitored closely for evidence of renal crisis. † Rituximab and cyclophosphamide recommended over IVIG, but IVIG may be preferred if there is high concern for infection. ILD, interstitial lung disease; IV, intravenous; IVIG, intravenous immune globulin; JAKi, JAK inhibitor; MDA-5, melanoma differentiation-associated protein 5; SARD, systemic autoimmune rheumatic disease.

concerns remain at any dose.[26–29] If glucocorticoids are considered, the lowest effective dose should be used, ideally <15 mg/day. The moderate certainty of evidence for harm[26–29] without clear evidence for efficacy led to a strong recommendation.

For people with SARD-ILD, we conditionally recommend mycophenolate, rituximab, cyclophosphamide, and azathioprineas first-line ILD treatment options.

Mycophenolate. Data on the use of mycophenolate in SSc-ILD suggest similar outcomes as cyclophosphamide but a more favorable adverse effect profile.[30–39] This and limited data in other diseases, combined with substantial clinical experience, led the Voting Panel to conditionally recommend mycophenolate as a preferred first-line ILD treatment option across SARDs.[30,32,33,40–44] However, alternative first-line ILD treatment options may be selected based on extrapulmonary manifestations or other factors, including patient preference.

Rituximab. Four trials and observational studies in people with SSc, RA, and IIM suggest that rituximab results in improvement or stabilization in FVC.[33,40,42,45–54] Rituximab may be preferred in the setting of inflammatory arthritis, myositis, or Sjögren neuropathy because of potential effectiveness for treating these manifestations. The Voting Panel expressed caution related to risk of infection, cost, and impact on immunogenicity of vaccines.

Five trials[36,52,54–56] in SSc-ILD and observational studies[12,27,58–68] in IIM-ILD, SSc-ILD, and RA-ILD suggest that cyclophosphamide results in FVC improvement or stabilization but with increased adverse events (eg, infection, cytopenias, hemorrhagic cystitis, infertility) compared with other agents. The Patient Panel noted a willingness to accept these risks in either life-threatening situations or for significant benefit. Although efficacy data resulted in recommending cyclophosphamide as a first-line ILD treatment option, the adverse effect profile led to cyclophosphamide being considered an "additional option" rather than preferred first-line treatment.

Azathioprine. The Voting Panel supported use of azathioprine as a first-line option across diseases, although in SSc-ILD, azathioprine was considered an "additional option" rather than "preferred" therapy because of limited evidence of effectiveness relative to other therapies in SSc-ILD (Figure 1).[30,33,42,66–68]

For people with SSc-ILD and MCTD-ILD, we conditionally recommend tocilizumab as a first-line ILD treatment option.

Tocilizumab resulted in FVC stabilization in two SSc trials compared with placebo.[69,70] Tocilizumab has a favorable adverse event profile relative to cyclophosphamide.[36,56,59–73] Thus, it is a preferred first-line treatment in SSc-ILD, specifically in those with an inflammatory phenotype (elevated C-reactive protein, progressive skin thickening) and early, diffuse disease. Tocilizumab was recommended as an additional option for first-line therapy in MCTD-ILD, particularly for patients with SSc features.[67] The Voting Panel was unable to reach consensus on using tocilizumab in RA-ILD, SjD-ILD, or IIM-ILD.

Table 2. Summary of Voting Panel decisions, certainty of evidence, PICO questions, and evidence that led to treatment recommendations*

Statement	Certainty of evidence	Based on the evidence reports of the following PICO(s)	Evidence table in Supplementary Materials 3, page(s)
For people with SARD-ILD other than SSc-ILD, we **conditionally** recommend glucocorticoids as a first-line ILD treatment.	Very low	36, 59, 60, 74, 75, 88, 89, 101, 102, 237	200, 201, 318–322, 371–375, 418–422, 465–469, 652
For people with SSc-ILD, we **strongly** recommend *against* daily glucocorticoids as a first-line ILD treatment.	Very low	36, 59, 60, 74, 75, 88, 89, 101, 102, 237	200, 202, 318–322, 371–375, 418–422, 652
For people with SARD-ILD, we **conditionally** recommend mycophenolate, azathioprine, rituximab, and cyclophosphamide as first-line ILD treatment options.	Very low	25, 33, 48, 49, 50, 52, 53, 55, 56, 60, 61, 65, 66, 68, 70	116, 179–189, 255–304, 309–313, 321–325, 335–349, 353–354, 359–361
For people with SSc-ILD and MCTD-ILD, we **conditionally** recommend tocilizumab as a first-line ILD treatment option.	Very low	50, 52, 68, 82, 95	292–294, 298–300, 353–355, 401–403, 440–444
For people with SARD-ILD, we **conditionally** recommend *against* leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.	Very low	27, 28, 31, 32, 46, 47, 51, 54, 62, 63, 67, 69, 77, 78, 81, 83, 91, 92, 94, 96	143–152, 170–179, 249–254, 295–298, 305–308, 325–330, 350–352, 356–358, 378–384, 398–400, 404–406, 425–432, 436–439, 444–447
For people with SjD-ILD, IIM-ILD, and MCTD-ILD, we **conditionally** recommend *against* nintedanib as a first-line ILD treatment option.	Very low	38, 56, 71, 85, 98, 104	203–223, 309–313, 362–366, 409–413, 450–454, 477–480
For people with SSc-ILD, we **conditionally** recommend nintedanib as a first-line ILD treatment option.	Very low	38, 56, 71, 85, 98, 104	203–223, 309–313, 362–366, 409–413, 450–454, 477–480
For people with RA-ILD, the Panel was not able to come to consensus on whether to recommend nintedanib as a first-line ILD treatment option.	Very low	38, 56, 71, 85, 98, 104	203–223, 309–313, 362–366, 409–413, 450–454, 477–480
For people with SARD-ILD, we **conditionally** recommend *against* pirfenidone as a first-line ILD treatment option.	Very low	39, 57, 72, 86, 99	224–229, 313–315, 366–368, 413–415, 455–461
For people with SARD-ILD receiving mycophenolate without evidence of ILD progression, we **conditionally** recommend *against* adding nintedanib or pirfenidone to mycophenolate.	Very low	42, 43	234–241
For people with SARD-ILD, we **conditionally** recommend *against* upfront combination of nintedanib or pirfenidone with mycophenolate over mycophenolate alone as first-line ILD treatment options.	Very low	44, 45	242–248
For people with IIM-ILD, we **conditionally** recommend JAKi as a first-line ILD treatment option.	Very low	35, 55, 70, 84, 97	197–199, 359–362, 407, 408, 448, 449
For people with IIM-ILD, we **conditionally** recommend CNIs as a first-line ILD treatment option.	Very low	30, 50, 66, 80, 93	162–169, 292–294, 346–349, 390–397, 433–435
For people with SARD-ILD, we **conditionally** recommend *against* IVIG or plasma exchange as first-line ILD treatment options.	Very low	40, 41, 58, 61, 73, 76, 87, 90, 100, 103	230–233, 316, 317, 323–325, 369, 370, 376–378, 416–418, 423, 424, 462–464
For people with SARD-associated ILD, we **conditionally** recommend optimal medical management over referral for stem cell or lung transplantation as first-line ILD treatment.	Very low	105, 106	481–489
For people with SARD-ILD with progression despite first ILD therapy, we **conditionally** recommend *against* adding glucocorticoids, and in people with SSc-ILD, we strongly recommend *against* adding glucocorticoids.	Very low	122, 123	515, 516
For people with SARD-ILD progression after first ILD therapy, we **conditionally** recommend using mycophenolate, rituximab, cyclophosphamide.	Very low	111, 112, 113, 115, 116, 118, 119, 121, 127, 128, 130, 131, 133, 134, 136, 139, 142	497–502, 504–508, 510–512, 514, 521–524, 526–528, 530–532, 534, 537, 540

(Continued)

Table 2. (*Cont'd*)

Statement	Certainty of evidence	Based on the evidence reports of the following PICO(s)	Evidence table in Supplementary Materials 3, page(s)
For people with SARD-ILD progression after first ILD therapy, we **conditionally** recommend adding nintedanib.	Very low	107, 148, 161	490–493, 547, 561
For people with RA-ILD progression after first ILD therapy, we **conditionally** recommend adding pirfenidone.	Very low	108, 120, 135, 149, 162	494, 513, 533, 548, 562
For people with SSc-ILD, MCTD-ILD, RA-ILD progression after first ILD therapy, we **conditionally** recommend adding tocilizumab.	Very low	145	544
For people with SARD-ILD other than IIM-ILD, with ILD progression after first ILD therapy, we **conditionally** recommend *against* adding CNIs.	Very low	143	541, 542
For people with IIM-ILD progression after first ILD therapy, we **conditionally** recommend adding CNIs.	Very low	143, 156	541, 542, 555
For people with SARD-ILD progression after first ILD therapy, we **conditionally** recommend adding JAKi over adding azathioprine.	Very low	147	546
For people with SARD-ILD progression after first ILD therapy, we **conditionally** recommend adding cyclophosphamide over adding JAKi.	Very low	160	559, 560
For people with IIM-ILD and MCTD-ILD progression after first ILD therapy, we **conditionally** recommend adding IVIG.	Very low	136, 150, 163	534, 549, 563
For people with SARD-ILD progression after first ILD therapy, we **conditionally** recommend *against* using plasma exchange.	Very low	139, 153, 166	537, 552, 555
For people with SSc-ILD progression after first ILD therapy, we **conditionally** recommend referral for stem cell transplantation and/or lung transplantation.	Very low	167, 168	568, 569
For people with SARD other than SSc and RP-ILD, we **conditionally** recommend pulse intravenous glucocorticoids as first-line RP-ILD treatment.	Very low	169, 170, 190, 191, 205, 206, 232, 233	570, 571, 595, 596, 616, 617, 643, 644
For people with SSc and RP-ILD, the Panel could not come to consensus on glucocorticoids as first-line RP-ILD treatment.	Very low	169, 170, 190, 191, 205, 206, 232, 233	570, 571, 595, 596, 616, 617, 643, 644
For people with SARD and RP-ILD, we **conditionally** recommend rituximab, cyclophosphamide, IVIG, mycophenolate, CNIs, and JAKi as first-line RP-ILD treatments.	Very low	180, 181, 184, 186, 189, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 207, 210, 211, 215, 224, 228, 231	583–586, 589, 591, 594, 598–618, 621–623, 626, 635, 639, 642
For people with SARD and RP-ILD, we **conditionally** recommend *against* nintedanib or pirfenidone as a first-line RP-ILD treatment.	Very low	171, 173, 175, 177, 178, 179, 182, 183, 185, 187, 195, 199, 202, 210, 211, 226, 229	572, 574, 576, 578–582, 587, 588, 590, 592, 600–601, 609, 613, 621, 622, 637, 640
For people with SARD-ILD and RP-ILD, we **conditionally** recommend *against* plasma exchange as first-line RP-ILD treatment.	Very low	192, 221, 234	597, 634, 645
For people with SARD-ILD other than SSc-ILD, and RP-ILD, we **conditionally** recommend dual combination therapy over monotherapy as first-line RP-ILD treatment.	Very low	235	646–648
For people with SSc-ILD and RP-ILD, we **conditionally** recommend *against* dual combination therapy[a] over monotherapy as first-line RP-ILD treatment.	Very low	235	646–648
For people with confirmed or suspected MDA-5 RP-ILD, we **conditionally** recommend triple combination therapy over monotherapy as first-line RP-ILD treatment.	Very low	236	649–651

(Continued)

Table 2. (*Cont'd*)

Statement	Certainty of evidence	Based on the evidence reports of the following PICO(s)	Evidence table in Supplementary Materials 3, page(s)
For people without high suspicion for MDA-5 RP-ILD, we **conditionally** recommend adding IVIG to monotherapy or dual combination therapy as first-line RP-ILD treatment.	Very low	238	653–657
For people without high suspicion for MDA-5 RP-ILD, we **conditionally** recommend *against* adding IVIG to triple therapy as first-line RP-ILD treatment.	Very low	238	653–657
For people without high suspicion for MDA-5 RP-ILD, we **conditionally** recommend adding IVIG to monotherapy, dual or triple combination therapy, as subsequent RP-ILD treatment.	Very low	238	653–657
For people without high suspicion for MDA-5 RP-ILD, we **conditionally** recommend adding plasma exchange to monotherapy or dual combination therapy as first-line RP-ILD treatment.	Very low	238	653–657
For people without high suspicion for MDA-5 RP-ILD, we **conditionally** recommend adding plasma exchange to monotherapy or dual combination therapy as subsequent RP-ILD treatment.	Very low	238	653–657
For people with SARD and RP-ILD, we **conditionally** recommend *against* referral for stem cell transplantation over optimal medical management as first-line RP-ILD treatment.	Very low	240	661
For people with SARD and RP-ILD, we **conditionally** recommend early referral for lung transplantation over later referral after progression on optimal medical management.	Very low	241	662

* CNI, calcineurin inhibitor; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; JAKi, JAK inhibitor; MCTD, mixed connective tissue disease; MDA-5, melanoma differentiation-associated protein 5; PICO, population, intervention, comparator, and outcomes; RA, rheumatoid arthritis; RP, rapidly progressive; SARD, systemic autoimmune rheumatic disease; SjD, Sjögren disease; SSc, systemic sclerosis; TNFi, tumor necrosis factor inhibitor.
[a] Monotherapy may include oral prednisone/intravenous methylprednisolone, mycophenolate, azathioprine, CNIs, rituximab, or cyclophosphamide. Dual combination therapy refers to simultaneous use of glucocorticoids and one of the above therapies. Triple combination therapy refers to simultaneous use of glucocorticoids and two of the above therapies.

For people with SARD-ILD, we conditionally recommend *against* leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.

Leflunomide. Leflunomide has been associated with development or worsening of ILD in rare cases. There is uncertain benefit on ILD outcomes.[31,74–78]

Methotrexate. Although methotrexate can rarely be associated with idiosyncratic pneumonitis, observational data suggest that methotrexate is not associated with progression of existing ILD.[75,79,80] Evidence on benefit for ILD, however, is lacking. Methotrexate may be continued in patients with ILD who are receiving it for extrapulmonary manifestations, but methotrexate should be stopped if there is concern for methotrexate pneumonitis, and some panelists would stop if ILD developed while on methotrexate.

Abatacept. Studies suggest no worsening of ILD with abatacept,[76,77,81,82] and discontinuation because of ILD is not necessary, but efficacy of abatacept for ILD is uncertain.[77,78,82–87]

TNFi. There are no data demonstrating a beneficial effect of TNFi on SARD-ILD, but observational data of low quality suggest harm or no effect.[31,88–93] TNFi can be used for extrapulmonary manifestations; however, some panelists would stop TNFi if ILD developed while on TNFi.

For people with SSc-ILD, we conditionally recommend nintedanib as a first-line ILD treatment option.

Trial evidence of low certainty supports nintedanib use in SSc-ILD. However, due to the attenuation of FVC decline rather than stabilization or improvement in published studies, lack of efficacy for non-ILD SARD manifestations, adverse effects (especially diarrhea), and cost, immunosuppressive medications were favored over nintedanib, with nintedanib recommended as an "additional" rather than a "preferred" option for first-line treatment.

For people with SjD-ILD, IIM-ILD, and MCTD-ILD, we conditionally recommend *against* nintedanib as a first-line ILD treatment option.

Evidence for efficacy of nintedanib in SjD-ILD, IIM-ILD, and MCTD-ILD is limited, and there are concerns regarding cost, adverse effects, and a preference for immunosuppressive therapies as first-line treatment. Some panelists would, however, consider using nintedanib for patients with a UIP pattern of ILD irrespective of SARD.

For people with RA-ILD, the Panel could not come to consensus on whether to recommend nintedanib as a first-line ILD treatment option.

Participants with RA-ILD in the INBUILD study were selected for progressive ILD and may not reflect most patients with RA-ILD in clinical practice.[8] Enthusiasm for nintedanib was limited given cost and potential adverse effects. Some Panelists consider nintedanib as a first-line ILD therapy option in patients with RA-ILD with a fibrotic/UIP pattern.

For people with SARD-ILD, we conditionally recommend *against* pirfenidone as a first-line ILD treatment option.

Limited evidence, adverse effects, and cost led to this recommendation.[91–95]

For people with SARD-ILD receiving mycophenolate without evidence of ILD progression, we conditionally recommend *against* adding nintedanib or pirfenidone to mycophenolate.

In considering the role of sequential combination therapy (ie, nintedanib or pirfenidone after starting mycophenolate, even in absence of ILD progression), cost, adverse effect profile, and limited data on efficacy in patients without evidence of progression on mycophenolate led to this recommendation.

For people with SARD-ILD, we conditionally recommend *against* upfront combination of nintedanib or pirfenidone with mycophenolate over mycophenolate alone as first-line ILD treatment options.

As with sequential therapy, there are concerns about cost and adverse effects from simultaneous use of both an antifibrotic and mycophenolate in those without progression on mycophenolate. The Patient Panel agreed, noting a willingness to tolerate adverse effects for crucial treatments but that gastrointestinal adverse effects could significantly impact QoL. Similar principles apply to upfront combinations of antifibrotics with other immunosuppressive therapies.

For people with IIM-ILD, we conditionally recommend JAKi as a first-line ILD treatment option.

For people with SARD-ILD other than IIM-ILD, we conditionally recommend *against* JAKi as a first-line ILD treatment option.

Indirect evidence from one observational study of anti-MDA-5 melanoma differentiation-associated protein 5 (MDA-5) associated ILD (not RP-ILD) suggested lower death rates with tofacitinib compared to tacrolimus.[86,91–95,107] With emerging evidence and increasing experience using JAKi in MDA-5-ILD, JAKi were recommended as an additional option, although not a preferred first-line therapy. Given lack of data and experience, we recommend against JAKi as first-line therapy for ILD associated with other SARDs.

For people with IIM-ILD, we conditionally recommend CNIs as a first-line ILD treatment option.

For people with SARD-ILD other than IIM-ILD, we conditionally recommend *against* CNIs as a first-line ILD treatment option.

Observational studies suggest benefits of CNIs for IIM-ILD.[12,16,96–98,104–106] These data, rapid onset of action, and lower cost led to a recommendation for CNIs as a first-line ILD treatment option for IIM-ILD. CNIs may be used particularly in MD-A-5-ILD or more severe forms of ILD at presentation. CNIs have potential renal toxicity, and providers may have less experience with dosing and monitoring (Table 3). The Panel preferred use of tacrolimus over cyclosporine because of perceived improved effectiveness. Given limited data, experience, and dosing and toxicity concerns, we recommend against CNIs as first-line therapy for other SARD-ILDs.[12,16,96–98]

For people with SARD-ILD, we conditionally recommend *against* IVIG or plasma exchange as first-line ILD treatment options.

IVIG is effective for myositis and dysphagia and may be used in the acute setting if infection is a concern. However, because of limited ILD efficacy data and experience, we recommend against IVIG and plasma exchange.[99–101]

For people with SARD-associated ILD, we conditionally recommend optimal medical management over referral for stem cell or lung transplantation as first-line ILD treatment options.

Indirect evidence from three stem cell transplantation (SCT) trials in SSc provided only low-certainty evidence because of significant loss of follow-up, small sample size, limited number of events, and different SCT protocols. SCT should be prioritized for centers with strong SSc-ILD experience and demonstrated positive outcomes to minimize differences in adverse effects and death risk. Lung transplantation should be considered after progression on therapy. Early referral for lung transplantation evaluation should be reserved for patients if presenting with advanced disease.

Recommendations for management of SARD-ILD progression despite first-line ILD treatment

For each recommendation below, first ILD therapy refers to any prior therapy and excludes the mentioned potential intervention. The term "using" implies "adding or switching" unless otherwise specified. A hierarchy of treatment options (Figure 2) has been established, but the order of therapy may vary because of patient factors and preferences. RP-ILD will be considered separately.

For people with SSc-ILD progression despite first ILD treatment, we strongly recommend *against* using long-term glucocorticoids, and in other SARD-ILD, we conditionally recommend *against* using long-term glucocorticoids.

Table 3. Medication toxicity and monitoring guidance*

Medication	Notable toxicities	Starting doses and frequency	Monitoring
Azathioprine	Hepatotoxicity, leukopenia, rarely pancreatitis	Starting at 50 mg per day PO and gradually increasing to a therapeutic dose of 2–3 mg/kg/day	CBC with differential at baseline and LFTs 2–3 weeks after starting and 2–3 weeks after any dose increase; every 3 months once on a stable dose
Cyclophosphamide	Marrow suppression, infertility, hemorrhagic cystitis, need for pregnancy avoidance; long term—malignancy, including bladder cancer	Intravenous: 500–750 mg/m^2 IV every 4 weeks for 6 months	CBC with differential and urinalysis at baseline; with intravenous dosing, CBC with differential 10–14 days after administration and just before next dose
		Oral: starting at 50–150 mg per day with target dose of 2 mg/kg per day (up to a maximum of 200 mg per day) for 6 months; some experts use a maximum dose of 100 mg daily	With oral dosing, CBC with differential 10–14 days after starting and 10–14 days after any dose increase; every 4 weeks on stable dosing
			Urinalysis every 4–8 weeks on stable dosing (IV or oral); once treated with cyclophosphamide, annual urine cytology
Cyclosporine	Infection, hypertension, nephrotoxicity, hyperkalemia, hepatotoxicity, neurotoxicity, gingival hyperplasia, thrombotic microangiopathy, malignancy, hirsutism	3 mg/kg/day[13] PO adjusted for the target trough levels between 100 and 150 ng/mL[14]	Baseline BP, serum creatinine, BUN, CBC, serum magnesium, potassium, uric acid, lipid profile; monitor BP, CBC, serum creatinine, and levels of BUN, uric acid, potassium, lipids, and magnesium every other week during the first 3 months of treatment, monthly monitoring after the first 3 months
Glucocorticoids: methylprednisolone and prednisone	Hyperglycemia, hypertension, mood disturbances, osteoporosis, avascular necrosis	Pulse: methylprednisolone 1 g IV daily for 3 days	Blood pressure and serum glucose, DEXA scan if ≥3 months of glucocorticoids anticipated[15]
		Prednisone 1 mg/kg/day PO	
IVIG	Aseptic meningitis, increased risk of VTE, renal insufficiency, hemolytic anemia	2 g/kg IV divided over 2–5 days every 4 weeks	IgA level before initiation; renal function before first infusion and at regular intervals; monitoring for anaphylaxis during infusion, especially in patients with IgA-deficiency, and thromboembolic events
JAKi (tofacitinib, baricitinib, upadacitinib)	Leukopenia, herpes zoster, black box warning regarding MACE, malignancy	Tofacitinib: immediate release tablet, 5 mg PO twice daily; extended-release tablet, 11 mg PO daily	Hepatitis B virus infection, hepatitis C virus infection, and latent TB screening before initiation; CBC with differential and CMP at baseline, 4–8 weeks after starting, and every 3 months thereafter; lipids at baseline, 4–8 weeks after starting, then annually
		Baricitinib: 2 mg PO daily	
		Upadacitinib: 15 mg PO daily	
Mycophenolate	Marrow suppression, hepatotoxicity; black box warning regarding pregnancy	Mycophenolate mofetil: starting at 500 mg PO twice daily and gradually increasing to a therapeutic dose of 1,000–1,500 mg twice daily	CBC with differential and CMP at baseline, 2–3 weeks after starting and 2–3 weeks after any dose increase, and every 3 months once on a stable dose; full body skin examination, preferably by a dermatologist, annually
		Mycophenolic acid: starting at 360 mg PO twice daily and gradually increasing to a therapeutic dose of 720–1,080 mg twice daily	
Nintedanib	Hepatotoxicity, diarrhea, increased risk of CV events, potential increased risk of bleeding	100–150 mg PO every 12 hours	LFTs every month for 3 months, then every 3 months; monitor for diarrhea and weight loss

(Continued)

Table 3. (*Cont'd*)

Medication	Notable toxicities	Starting doses and frequency	Monitoring
Pirfenidone	Rash, diarrhea, nausea, abdominal pain, photosensitivity, weight loss, upper respiratory tract infection, dizziness	Days 1 to 7: 267 mg 3 times per day; days 8 to 14: 534 mg 3 times per day; day 15 and after: 801 mg 3 times per day	LFTs at baseline, every month for the first 6 months, then every 3 months thereafter; monitor for photosensitivity and weight loss
Rituximab	Cytopenias, infection, hepatitis B reactivation; black box warning for PML	1 g IV every 2 weeks for 2 doses; may be repeated every 24 weeks as needed	Hepatitis B virus infection, hepatitis C virus infection, and latent TB screening before initiation; CBC with differential at baseline and at 2- to 4-month intervals; monitor for infusion reactions
Tacrolimus	Leukopenia, renal failure, neurotoxicity	Dosing: 0.075 mg/kg/day adjusted for the target whole-blood trough levels between 5 and 10 ng/mL[16]; some experts use a maximum trough level of 6 ng/mL	Trough tacrolimus level, CMP, magnesium, phosphorus monitored 1–2 times per week for the first month, monthly for 3 months, then every 2–3 months; monitor BP
Tocilizumab	Transaminitis, hyperlipidemia, bowel perforation	162 mg subcutaneously weekly	Latent TB screening before initiation; CBC with differential at baseline, 4–8 weeks after starting therapy, and every 3 months thereafter; ALT/AST, alkaline phosphatase, and total bilirubin at baseline, every 4–8 weeks after starting therapy for the first 6 months, and every 3 months thereafter; lipids at baseline, 4–8 weeks after starting therapy, 6 months after starting therapy, then annually

* ALT, alanine transaminase; AST, aspartate transaminase; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; CV, acrdiovascular; DEXA, dual-energy X-ray absorptiometry; IV, intravenous; IVIG, intravenous immunoglobulin; JAKi, JAK inhibitor; LFT, liver function test; MACE, major adverse cadiovascular events; PML, progressive multifocal leukoencephalopathy; PO, per os; TB, tuberculosis; VTE, venous thromboembolism.

Addition of long-term glucocorticoids (eg, >3 to 6 months) should not be relied upon for treating progressive ILD. Glucocorticoids may have a short-term role in patients with flares or as a bridge for those warranting a more definitive therapy change. The recommendation against glucocorticoids in SSc-ILD is strong because of moderate-certainty evidence of risk of SRC and very low-certainty evidence of benefit.

For people with SARD-ILD progression despite first ILD treatment, we conditionally recommend mycophenolate, rituximab, cyclophosphamide, and nintedanib as treatment options.

Mycophenolate. If there is progression on first-line therapy, switching to mycophenolate is recommended over other treatment options, based on two trials and observational studies in SSc-ILD and RA-ILD of low certainty[30–39] and concerns about cyclophosphamide toxicity.

Rituximab. Indirect evidence from four trials and observational studies[33,40,42,45–54] suggests FVC stabilization or improvement in people with SSc-ILD, MCTD-ILD, IIM-ILD, RA-ILD, and SjD-ILD. Some panelists add rituximab to mycophenolate for SSc-ILD and IIM-ILD, while others switch to rituximab, depending on patients' risk factors and preferences.

Cyclophosphamide. Indirect evidence from five trials[36,52,54–56] in SSc-ILD and observational studies[12,27,60–68] in IIM-ILD, SSc-ILD, and RA-ILD suggests FVC stabilization or improvement with cyclophosphamide, making it a second-line option despite its side effect profile.

Nintedanib. Nintedanib may be added, particularly for those with progressive fibrosing disease on HRCT chest. Concerns were raised that nintedanib only slows FVC decline, at best, and has frequent gastrointestinal side-effects and cost.

For people with RA-ILD progression despite first ILD treatment, we conditionally recommend adding pirfenidone.

For people with SARD-ILD other than RA-ILD progression despite first ILD treatment, we conditionally recommend *against* adding pirfenidone.

Trials of pirfenidone in RA-ILD and SSc-ILD are underpowered but suggest that pirfenidone may attenuate FVC progression.[91–95] Pirfenidone can be considered in RA-ILD, particularly with a UIP pattern.

For people with SSc-ILD, MCTD-ILD, and RA-ILD progression despite first ILD treatment, we conditionally recommend tocilizumab as a treatment option.

For people with SjD-ILD and IIM-ILD progression despite first ILD treatment, we conditionally recommend *against* tocilizumab as a treatment option.

Although there is randomized controlled trial evidence for tocilizumab in SSc-ILD, it was studied primarily in early

Table 4. Additional integrative and pharmacologic interventions that may be considered in the care of people with SARD-ILD*

Interventions	Examples
Integrative	
Exercise	Aerobic, resistance training, yoga, tai chi
Palliative care	Symptom treatment (eg, cough, pain, air hunger), end of life planning[17,18]
Physiotherapy	Chest physiotherapy, airway clearance, incentive spirometry
Pulmonary rehabilitation	Cardiopulmonary rehabilitation, resistance training[19]
Smoking cessation	Smoking cessation program
Supplemental oxygen	Oxygen administration by nasal prongs
Pharmacologic	
Gastroesophageal reflux management	Proton pump inhibitors, H2 blockers[20,21]
PJP prophylaxis	Trimethoprim sulfamethoxazole
Promotility agents	Domperidone
Vaccines	MMR, influenza, COVID-19, pneumococcus, varicella zoster, RSV[22,23]

* ILD, interstitial lung disease; MMR, measle, mumps, rubella; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; SARD, systemic autoimmune rheumatic disease.

SSc-ILD.[69,70] Adding or switching to tocilizumab may be an option in early progressive SSc-ILD, diffuse skin involvement, and elevated acute phase reactants and in MCTD-ILD with an SSc phenotype. Tocilizumab was conditionally recommended in RA-ILD despite limited evidence, given its established use for articular disease and favorable safety profile compared to cyclophosphamide.

For people with IIM-ILD progression despite first ILD treatments, we conditionally recommend CNIs as a treatment option.

For people with SARD-ILD other than IIM-ILD progression despite first ILD treatments, we conditionally recommend *against* CNIs as a treatment option.

CNIs have been beneficial in refractory IIM-ILD, particularly those with anti-synthetase syndrome or MDA-5-ILD.[12,102,103] Although the Panel preferred mycophenolate and rituximab over CNIs, CNIs are a treatment option for IIM-ILD with progression after first ILD treatment. Given limited data and experience, CNIs are not recommended in other SARD-ILDs.

For people with IIM-ILD progression despite first ILD treatment, we conditionally recommend JAKi as a treatment option.

Emerging evidence suggests that JAKi are a potential treatment for IIM-ILD. Given limited data, however, other treatments, including cyclophosphamide, were recommended over JAKi.

For people with IIM-ILD and MCTD-ILD progression despite first ILD treatment, we conditionally recommend adding IVIG as a treatment option.

Observational studies report IVIG use in IIM-ILD.[97,98] Panelists reported using IVIG in IIM-ILD and myositis predominant–MCTD-ILD, particularly. IVIG may be useful when rapid onset of action is desired, eg, presence of severe respiratory muscle weakness.

For people with SARD-ILD progression despite first ILD treatment, we conditionally recommend *against* using plasma exchange.

Data supporting use of plasma exchange are limited to small observational studies, and plasma exchange has potential risks.

For people with SSc-ILD progression despite first ILD treatment, we conditionally recommend referral for SCT and/or lung transplantation.

Although SCT has been evaluated in three trials of low evidence certainty, the associated harms are understudied. The Panel was concerned about toxicity and the small number of centers that are well-equipped for its safe performance. Patient Panelists would consider transplantation in carefully selected cases if there was potential benefit. Although referral for SCT may be considered in those with ILD progression despite one or more ILD medications, the Panel did not reach consensus on optimal referral timing. Because there are a limited number of centers offering lung transplantation, referral should occur before a patient deteriorates and is no longer eligible.

Recommendations for management of SARD with RP-ILD

For people with SARD and RP-ILD, we conditionally recommend pulse intravenous methylprednisolone as first-line RP-ILD treatment.

Intravenous pulse methylprednisolone is recommended as first-line RP-ILD treatment because of rapid onset of action. Usual practice is to use intravenous glucocorticoids followed by high-dose oral prednisone. Glucocorticoids are typically administered with other immunosuppressive agents. RP-ILD in SSc is rare and may have an overlap syndrome or MCTD. Generally, we strongly recommend against use of glucocorticoids in SSc, but in the rare occurrence of RP-ILD in a person with SSc, there was no Panel consensus on whether to recommend glucocorticoids. Therapy may be warranted given the life-threatening nature of RP-ILD, despite the potential risk for SRC with glucocorticoids. We suggest an individualized approach in rare instances of RP-ILD in SSc.

For people with SARD and RP-ILD, we conditionally recommend rituximab, cyclophosphamide, IVIG, mycophenolate, CNIs, and JAKi as first-line RP-ILD treatment options.

Rituximab. The RECITAL trial, comparing rituximab and cyclophosphamide in severe and progressive IIM-ILD, SSc-ILD, and MCTD-ILD, demonstrated similar mortality rates and FVC but higher rates of gastrointestinal and nervous system disorders

in the cyclophosphamide group with similar discontinuation rates in the two treatment groups.[52] The peak efficacy of rituximab is after several months of treatment, with onset of effect beginning sooner. There was concern about infection risk with rituximab because immunosuppressive effects last six months compared with one month with cyclophosphamide. The Panel conditionally recommended rituximab over mycophenolate, azathioprine, CNIs, and JAKi for RP-ILD.

Cyclophosphamide. The Panel preferred intravenous over oral administration and voted conditionally for cyclophosphamide over mycophenolate and azathioprine. There was no consensus on cyclophosphamide versus rituximab except for MDA-5 RP-ILD, for which rituximab was preferred over cyclophosphamide. Patient Panelists were willing to accept significant adverse effects in the case of life-threatening illness if risks were clearly communicated but acknowledged that specific patient concerns (eg, fertility) may vary substantially.

IVIG. Panelists reported using IVIG with pulse methylprednisolone in RP-ILD, noting a lower infection risk, particularly important in patients who are critically ill or intubated.[99] IVIG is in limited supply and costly; it should not be used long term without clear clinical need. The Panel voted conditionally for rituximab and cyclophosphamide over IVIG but noted that IVIG may be used initially when infection risk is of particular concern.

Mycophenolate. Based on very low-certainty randomized trial evidence,[26–29,31,32] experience, and tolerability of mycophenolate in SARD-ILD, the Panel recommends its use in RP-ILD.

CNIs. Tacrolimus is increasingly used in IIM RP-ILD based on observational studies suggesting improved survival in IIM-ILD (non–RP-ILD).[12,16,96–98,104,106] The Panel voted conditionally for rituximab, cyclophosphamide, and mycophenolate over CNIs but voted conditionally for CNIs over azathioprine. Some panelists would consider tacrolimus over mycophenolate in MDA-5 RP-ILD.

JAKi. Observational data suggest possible effectiveness of JAKi in those with MDA-5-ILD but without RP-ILD, and small studies report a possible benefit of adding JAKi to other therapy in refractory cases.[86,107–109] Given the limited data and experience, the Panel conditionally voted for cyclophosphamide, rituximab, and mycophenolate over JAKi.

For people with SARD and RP-ILD, we conditionally recommend *against* methotrexate, leflunomide, azathioprine, TNFi, abatacept, tocilizumab, nintedanib, pirfenidone, and plasma exchange as first-line RP-ILD treatment options.

There was neither evidence nor experience to support the use of these therapies in RP-ILD. Azathioprine is not typically used for RP-ILD. Low-quality observational data suggest that combination therapy with plasma exchange may result in a reduction in antibodies, improved oxygen exchange, and survival.[100,101] Concerns were raised about cost, and availability is limited to specialized centers. Plasma exchange should not be used as first-line RP-ILD therapy but reserved as salvage therapy. If used, it is important to avoid rituximab or IVIG removal by plasma exchange.

For people with RP-ILD, we conditionally recommend upfront combination therapy (triple therapy for those with confirmed or suspected MDA-5 and double or triple therapy for those without confirmed or suspected MDA-5) over monotherapy as first-line treatment.

RP-ILD carries a substantial risk of death, and several observational studies have suggested benefit from treatment with upfront combination therapy.[12,99–101,107,110–112] A study of MDA-5-ILD evaluating combination cyclophosphamide, tacrolimus, and glucocorticoids demonstrated a beneficial effect on survival compared to a sequential step-up approach.[12] One study found adding IVIG to standard immunosuppressive medications in MDA-5 RP-ILD resulted in lower all-cause death rate compared with standard therapy.[99] There is insufficient evidence to recommend one specific treatment regimen, and treatment selections may depend on disease severity, whether the person has suspected MDA-5 RP-ILD, and infection. Typically, initial combination therapy involves glucocorticoids with one or two additional agents recommended for RP-ILD, especially rituximab, cyclophosphamide, IVIG, tacrolimus, mycophenolate, or JAKi (Figure 3). Adding other agents may be considered for those who are not responding to therapy. There are limited data on adding plasma exchange to combination therapy in refractory cases.[12,100,101,111–114]

For people with SARD and RP-ILD, we conditionally recommend *against* referral for SCT over optimal medical management as first-line RP-ILD treatment.

There was indirect evidence from three trials. The Voting Panel had concerns about the ability of people with RP-ILD to tolerate SCT.

For people with SARD and RP-ILD, we conditionally recommend early referral for lung transplantation over later referral after progression on optimal medical management.

There is a limited opportunity for lung transplantation, and the pre-transplantation evaluation takes time. Options for medical therapy may be swayed by a patient's candidacy for lung transplantation. The need for high-flow oxygen is a marker of severity that warrants transfer to a transplantation center. Early referral to a transplantation center is warranted even if not local for the patient. Patient Panelists preferred early referral for lung transplantation and were agreeable to traveling away from home for potentially life-saving measures.

DISCUSSION

We present recommendations for first-line ILD treatment, treatment for ILD progression despite first-line treatment, and treatment of RP-ILD. The Panel voted on paired comparisons of treatment options resulting in a hierarchy of "preferred" and "additional" options for ILD treatment based on Voting and

Patient Panel deliberations. Although mycophenolate was generally favored as a first-line ILD treatment for all diseases, patient- and disease-specific factors may lead to selection of a different treatment within the "menu of options" provided. For example, in people with RA-ILD with active inflammatory arthritis, rituximab (also a preferred option) may be chosen, particularly considering potential benefits for death and possibly ILD by reducing disease activity. We provide this hierarchy to be transparent about how experts consider these options, particularly in the setting of low- to very low-certainty evidence. This hierarchy should not be used by insurers to mandate a specific order of prescribing. Clinicians must retain the latitude to prescribe recommended medications based on individual patient factors and preferences. This guideline emphasizes co-management of people with SARD-ILD by rheumatologists and pulmonologists.

Glucocorticoids should be considered separately from other treatments, and our two strong recommendations are against their use in SSc-ILD because of their association with SRC.[26–29] For the other diseases, short-term glucocorticoids may be considered; however, there are patients in whom glucocorticoids may not be necessary as a first-line therapy. In individuals with ILD progression, long-term glucocorticoid use should be avoided and reserved for short-term use, such as bridging to another therapy. The Panel advised against the use of methotrexate, leflunomide, TNFi, and abatacept for SARD-ILD treatment, although these treatments may be appropriate for extrapulmonary manifestations. Some panelists would stop these medications if ILD developed while using them.

Because most recommendations are conditional, shared decision-making that accounts for factors such as ILD severity, risk factors for progression, other disease manifestations, cost, and toxicity is crucial when choosing a medication within the range of recommended options. Co-management with pulmonologists is advised for initiation of ILD treatment, particularly to determine the need for treatment in asymptomatic patients with stable and mild ILD. Patient Panelists were willing to tolerate medication toxicity if there is potential for substantial benefit, particularly to prolong life.[7] However, they requested clear communication about potential toxicities and close collaboration with their providers when starting a medication to work through any adverse effects that develop.[7]

RP-ILD is a descriptive term of the modern era, initially coined to describe patients who go from being well to respiratory failure (needing high-flow oxygen or mechanical ventilation) within days to weeks. RP-ILD has been used primarily in the context of MDA-5-IIM. Historically, it was termed acute interstitial pneumonitis, but because of overlapping terminology, the meaning has been less clear. The Panel conceptualized RP-ILD in its original context. Note that PPF and PF-ILD differ from RP-ILD, and these terms are not interchangeable.[11]

Research is needed to better understand fibrotic, inflammatory, or mixed lung phenotypes, given that HRCT patterns of ILD (eg, nonspecific interstitial pneumonia, UIP) are often used to guide therapeutic decision-making. Investigation of tissue-level effects of therapeutics or development of predictive biomarkers might lead to more informed management decisions. Higher-certainty evidence is needed on the impact of therapeutics on patient-important outcomes, including harms. Research is needed among individuals who may be disproportionately affected by the diseases or face barriers to accessing care (eg, those with low income, women, and Black and Hispanic individuals). Although our recommendations are based on the best available evidence, in some instances, practice is changing in advance of data. For example, several expert centers use tacrolimus and IVIG in critically ill patients with RP-ILD, although published data are limited.

A limitation of this guideline was our inability to include other important affected patient groups, interventions, and outcomes. The scope of the guideline needed to be focused on what we considered to be the most critical of these. Additional integrative and pharmacologic interventions are summarized in Table 4 and could be considered patient by patient. The inclusion of pharmacists and stem cell or lung transplantation specialists would have further informed the Voting Panel. Although trial data were available, the certainty of evidence was frequently downgraded for small sample size, use of surrogate outcomes (eg, FVC), and evaluations in different groups than the diseases of interest. In addition to evidence, the Voting Panel deliberations considered clinical experience, patient values and preferences, disease burden, and access considerations, including cost.

In summary, we present guidelines for first-line treatment of SARD-ILD, treatment for ILD progression despite first ILD therapy, and treatment of RP-ILD in people with SARDs. This ACR guideline provides recommendations for ILD treatment decisions frequently faced in clinical practice.

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