SUPPLEMENTARY APPENDIX 5: Evidence Report/Summary

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis and 2018 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis

Introduction

Critical outcomes

- Each table reports the summary of findings from randomized trials and/or observational studies reporting the critical outcomes. The critical outcomes, as chosen by the Core Team, varied among the different subgroups of pediatric patients with JIA (polyarthritis, sacroiilitis/enthesitis) and/or uveitis.
- For polyarthritis and sacroiliitis/enthesitis, critical outcomes included quality of life measures, disease activity measures (pediatric ACR response, JADAS, active joint count, ESR/CRP, patient/parent global, active entheses count [enthesitis only], BASDAI [sacroiliitis/enthesitis only], BASFI [sacroiliitis/enthesitis only], other sacroiliitis/enthesitis-specific measures), ACR provisional criteria for clinical inactive disease, functional ability (CHAQ, PROMIS), joint damage requiring surgical intervention, and serious adverse events (e.g. hospitalization, infection, malignancy). An additional critical outcome for sacroiliitis was resolution of MRI findings consistent with active sacroiliitis.
- For uveitis, critical outcomes differed for questions related to screening, monitoring, and medication. For screening questions, critical outcomes included new diagnosis of uveitis and new diagnosis of uveitis with any ocular complications. For monitoring questions, critical outcomes included loss of control of uveitis and new complications due to inflammation. For medication questions, critical outcomes included loss of control of uveitis, incidence of loss of control of uveitis, control of uveitis at 1 month and 3 months, new ocular steroid complications (cataracts, glaucoma/increased IOP, infection), new ocular complications due to inflammation, incidence of uveitis, and recurrence of uveitis
- Note that serious adverse events are very rare, and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in randomized trials powered for efficacy outcomes that occur much more often.
- Not every study identified examined all critical outcomes. Each outcome was analyzed separately.

Interventions

- The following interventions were within the scope of this guideline:
    - NSAIDs (polyarthritis and sacroiliitis/enthesitis only)
    - Glucocorticoids (oral and intra-articular injections for polyarthritis and sacroiliitis/enthesitis; topical, oral, and intraocular injections for uveitis)
    - Non-biologic disease modifying anti-rheumatic drugs (DMARDs): this includes methotrexate, sulfasalazine, leflunomide (polyarthritis only), cyclosporine (uveitis only), mycophenolate (uveitis only)
    - TNF inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol)
    - Other biological response modifiers (OBRM): abatacept, tocilizumab, rituximab
    - Physical therapy, occupational therapy (polyarthritis and sacroiliitis/enthesitis only)

Systematic Literature Review

- While randomized controlled trials (RCTs) were the preferred source of evidence, observational studies that directly or indirectly addressed PICO questions with little or no RCT evidence were also included.

Quality Assessment

- Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
- Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
- Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
- Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
- Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.

- The level of evidence listed in this report for either an individual paper or a group of papers is not meant to be an absolute statement about the quality of the study (or studies) under consideration. Rather, the intention is to rate the paper(s) *in relation to the question being asked in this guideline*. Because of this, a very well conducted study might actually be rated down in this evidence report, possible reasons including that the population or intervention being studied does not completely match the population or intervention being examined by the PICO question in this guideline (in other words, downgrading for indirectness). The level of evidence may also be downgraded due to imprecision in the effect estimate (wide confidence intervals that cross the line of no effect, or a low number of patients or events). A combination of these factors may result in quality of evidence from a well-conducted study being rated as low.

Presentation of effects

- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction (10% - 5%/ 10%)
- The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). In general, for patients, the absolute effect is the most important.
- Relative effects for dichotomous outcomes in the tables are expressed as relative risk (RR) or odds ratio (OR). RR is the default effect size because it is more easily interpretable, but under some circumstances RRs can lead to impossible numbers when calculating absolute risk differences. In such instances ORs were used instead of RRs.
- In the tables, when RR or OR is specified, the first drug (e.g. etanercept vs abatacept) is the reference drug.

Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)

- Direct comparisons are situations where trials directly compare drug A to drug B within one of the patient subgroups covered in this guideline.
- Indirect comparisons: Some studies do not include a direct comparison of drugs or interventions specified in a given PICO question. An example of this is trial that compare drug A to placebo, or an observational study where all patients received drug A and a pre-post comparison is made.

Interpreting the evidence

- It is important to take into account the information presented specifically as it relates to the question of interest. For example, when the only evidence for a given PICO question is indirect due to the comparison or patient population, it appropriately gets downgraded for indirectness as shown under the column labeled “indirectness.” Also, if the 95% confidence interval around an effect size is wide and

crosses the line of no difference between treatments, the evidence for that outcome is downgraded due to imprecision. Study design and risk of bias also may result in downgrades in the quality of evidence. The overall quality of evidence takes all these factors into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to your decisions.

Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high quality evidence of important harm then a strong recommendation against the intervention may be appropriate.

Bibliography of included studies

- A complete list of studies included as evidence for this report appears at the end of this document, following Uveitis PICO 34. Shorter lists of studies included for each PICO question with an evidence base appear at the end of the summaries for each question

Polyarthritis

PICO 1: In children and adolescents with JIA and polyarthritis, should methotrexate subcutaneous (SQ) or methotrexate oral (PO) be recommended?

Summary**:** The literature search identified two randomized controlled trials (RCTs)[1][2] and six observational studies[3,4,5,6,7,8] that addressed this PICO question. The RCTs provided indirect evidence by comparing either methotrexate (PO) to placebo alone[1] or methotrexate (SQ) to methotrexate (SQ), etanercept, and prednisolone together.[2] The study by Giannini found significant differences between the number of joints with pain on motion (p= 0.016) and the number of joints with limited ROM (p= 0.04) that favored methotrexate (10 mg per square meter of body surface per week) over placebo (Table 1). However, the measures used in this study are inconsistent with other studies. Furthermore, there was no sub-analysis of polyarticular JIA patients; all patient scores were reported together. The criteria for enrollment was also vague in that the patients from the U.S. had to meet the ACR guidelines for a diagnosis of JRA, however patients from Europe were diagnosed based on unpublished criteria denoted as "criteria used in the Soviet Union and Eastern Europe." The study by Wallace (which used methotrexate SQ 0.5 mg/kg/week in both arms, maximum 40 mg) identified no statistically significant difference in clinically inactive disease at 6 months or 12 months of therapy (Table 2). The study did not meet the primary end point of a significant between-group difference in clinically inactive disease within 6 months of therapy and remission within 12 months. However, there was a significant difference in the number of patients who met ACR Pedi 70 at 4 months that favored early aggressive combination therapy (p=0.011). An open-label extension of this trial from 4 to 12 months consisted mostly of patients switched to aggressive therapy; 56% of patients achieved clinically inactive disease status.[3]

The observational studies provided direct drug comparisons (MTX SQ versus MTX PO). Three observational studies reported no significant differences in ACR 30/50/70[3], ACR score (not specified)[7] or response rate (defined as ≥50 reduction in joints with active arthritis and/or articular severity score).[8] Results for intolerance (Methotrexate Intolerance Severity Score (MISS) ≥6) indicated an association with MTX SQ in two studies and a similar trend in a third.[4][5][6] Two studies reporting on adverse events reported no differences between administration type.[3][8]

Quality of evidence across all critical outcomes: Very low

Table 1. Low-Dose Methotrexate compared to Placebo for polyarticular JIA

Bibliography: Giannini EH et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings		
№ of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality	Number of patients	Relative effect	Anticipated absolute effects

Table 1. Low-Dose Methotrexate compared to Placebo for polyarticular JIA

Bibliography: Giannini EH et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
(studies) Follow-up						of evidence	With Placebo	With Low-Dose MTX	(95% CI)	Risk with Placebo	Risk difference with Low-Dose MTX
Change in Articular Severity Score (composite of joint swelling, pain, tenderness, limitation of range of motion)											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	39	38	-	-	SMD **0.11 lower** (0.55 lower to 0.34 higher)
Change in number of joints with pain on ROM											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	39	38	**Favors Low-dose MTX**	-	SMD **1.34 lower** (1.84 lower to 0.85 lower)
Change in number of joints with tenderness											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	39	38	-	-	SMD **0.29 lower** (0.74 lower to 0.16 higher)
Change in duration of morning stiffness											

Table 1. Low-Dose Methotrexate compared to Placebo for polyarticular JIA

Bibliography: Giannini EH et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.12 lower** (0.57 lower to 0.32 higher)
Change in number of joints with active arthritis											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.17 lower** (0.62 lower to 0.27 higher)
Change in number of joints with limitation of motion											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⊕⊕◯◯ LOW	39	38	**Favors Low-dose MTX (10 mg/M² BSA)**	-	SMD **0.5 lower** (0.95 lower to 0.04 lower)
Change in number of joints with swelling											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.28 lower** (0.73 lower to 0.17 higher)

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. randomization not described, high dropout rate, subgroup analysis of JIA subtypes not performed

b. not applicable

c. study only uses only oral methotrexate and compares it to placebo rather than subcutaneous methotrexate.

d. Single study, wide 95% CI includes no difference

Table 2. Methotrexate, Etanercept, Prednisolone compared to Methotrexate alone for polyarticular JIA

Bibliography: Wallace CA et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2012; 64(6): 2012-21.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With MTX alone	**With MTX, ETA, Prednisolone**		**Risk with MTX alone**	**Risk difference with MTX, ETA, Prednisolone**
ACR Pediatric 70											
85 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	19/43 (44.2%)	30/42 (71.4%)	**OR 3.16** (1.28 to 7.77) **Favors combined treatment**	442 per 1,000	**273 more per 1,000** (61 more to 418 more)
Clinical inactive disease achieved at 6 mos											

Table 2. Methotrexate, Etanercept, Prednisolone compared to Methotrexate alone for polyarticular JIA

Bibliography: Wallace CA et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2012; 64(6): 2012-21.

Quality assessment							Summary of findings				
85 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	10/43 (23.3%)	17/42 (40.5%)	**RR 1.74** (0.90 to 3.35)	233 per 1,000	**172 more per 1,000** (23 fewer to 547 more)
Clinical Remission on Medication											
85 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	3/43 (7.0%)	9/42 (21.4%)	**RR 3.07** (0.89 to 10.57)	70 per 1,000	**144 more per 1,000** (8 fewer to 668 more)

OR: odds ratio; **RR**: risk ratio

Explanations

a. not applicable

b. study only uses subcutaneous and not oral methotrexate as discussed in the PICO question,

c. Single study, wide 95% CI includes no difference

Table 3. MTX SQ compared to MTX PO for polyarticular JIA

Klein A, et al. Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children With Juvenile Idiopathic Arthritis: An Observational Study With Patients From the German Methotrexate Registry. Arthritis Care Res. 2012;64(9):1349-1356.

Bulatovic M, Heijstek M, Verkaaik M, van Dijkhuizen E, Armbrust W, Hoppenreijs E, et al. High Prevalence of Methotrexate Intolerance in Juvenile Idiopathic Arthritis. Arthritis Rheum. 2011;63(7):2007-2013.

Certainty assessment							Summary of findings		
№ of participants	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Study event rates (%)**	**Relative effect (95% CI)**	**Anticipated absolute effects**

Table 3. MTX SQ compared to MTX PO for polyarticular JIA

Klein A, et al. Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children With Juvenile Idiopathic Arthritis: An Observational Study With Patients From the German Methotrexate Registry. Arthritis Care Res. 2012;64(9):1349-1356.

Bulatovic M, Heijstek M, Verkaaik M, van Dijkhuizen E, Armbrust W, Hoppenreijs E, et al. High Prevalence of Methotrexate Intolerance in Juvenile Idiopathic Arthritis. Arthritis Rheum. 2011;63(7):2007-2013.

Certainty assessment							Summary of findings				
(studies) Follow-up						**of evidence**	**With MTX PO**	**With MTX SQ**		**Risk with MTX PO**	**Risk difference with MTX SQ**
ACR 30, 6 months, subpopulation of polyarticular											
148 (1 observational study) Klein 2012	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	76/83 (91.6%) Median dose 0.4 mg/kg/ week	55/65 (84.6%) Median dose 0.42 mg/kg/ week	**OR 0.51** (0.18 to 1.41)	916 per 1,000	**69 fewer per 1,000** (254 fewer to 23 more)
ACR 50, 6 months, subpopulation of polyarticular											
148 (1 observational study) Klein 2012	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	69/83 (83.1%)	53/65 (81.5%)	**OR 0.90** (0.38 to 2.10)	831 per 1,000	**15 fewer per 1,000** (179 fewer to 81 more)
ACR 70, 6 months, subpopulation of polyarticular											
148 (1 observational study) Klein 2012	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	52/83 (62.7%)	43/65 (66.2%)	**OR 1.17** (0.59 to 2.30)	627 per 1,000	**36 more per 1,000** (129 fewer to 168 more)

Table 3. MTX SQ compared to MTX PO for polyarticular JIA

Klein A, et al. Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children With Juvenile Idiopathic Arthritis: An Observational Study With Patients From the German Methotrexate Registry. Arthritis Care Res. 2012;64(9):1349-1356.

Bulatovic M, Heijstek M, Verkaaik M, van Dijkhuizen E, Armbrust W, Hoppenreijs E, et al. High Prevalence of Methotrexate Intolerance in Juvenile Idiopathic Arthritis. Arthritis Rheum. 2011;63(7):2007-2013.

Certainty assessment							Summary of findings				
Serious adverse events											
411 (1 observational study) Klein 2012	serious [a]	not serious [b]	not serious	serious [d]	none	⊕◯◯◯ VERY LOW	3/259 (1.2%)	2/152 (1.3%)	**OR 1.14** (0.19 to 6.89)	12 per 1,000	**2 more per 1,000** (9 fewer to 63 more)
Intolerance (MTX Intolerance Severity Score (MISS) = / > 6)											
297 (1 observational study) Bulatovic 2011	serious [e]	not serious [b]	not serious	not serious	none	⊕◯◯◯ VERY LOW	98/220 (44.5%)	52/77 (67.5%)	**OR 2.59** (1.50 to 4.47) **Favors MTX oral (10.2 mg/m²/week)**	445 per 1,000	**230 more per 1,000** (101 more to 337 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Retrospective, non-randomized, no blinding

b. Not applicable

c. Single study. 95% CI includes the line of no difference.

d. Single study. Wide 95% CI includes the line of no difference.

e. Prospective, non-randomized, no blinding

Table 4. Additional Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5208, Franova, 2016	Prospective observational	12 months	55 patients with JIA (60% polyarticular)	MTX (45 parenteral, 10 oral) Median parenteral dose: 14.4 mg/m^2 Median oral dose: 11.7 mg/m^2	Parenteral form of MTX was not significantly associated with MTX intolerance (MISS ≥6)(OR 2.44, 95% CI 0.56 to 10.65; p=0.236), but the direction of effect suggested a trend toward higher intolerance with parenteral MTX.
Van Dijkhuizen 2016	Prospective observational	Median 21.0 months (IQR range 10.0 to 31.0) for intolerant	179 patients with JIA (51.3% polyarticular)	MTX (46 subcutaneous, 95 oral) Median dose: 12 mg/m^2/week 73 Intolerant patients (40.8%)	Multivariate logistic regression analysis indicated that subcutaneous form of MTX was significantly associated with MTX intolerance (MISS ≥6 plus at least one associative, anticipatory, or behavioral symptom) (OR 3.4, 95% CI: 1.2 to 10.0; p=0.02).
Zuber 2016	Prospective observational	12 months	126 patients with JIA (36% polyarticular)	MTX (126 oral at baseline; 32 switched to subcutaneous at 6 months) Mean oral dose: 12.6 mg/m^2 Mean subcutaneous dose: 12.8 mg/m^2	Oral MTX: At 6 months, 83 (65.9%) patients achieved ACR 30, and 40 (32%) patients achieved ACR 70. 32 (25%) children were intolerant or reluctant to take oral MTX and switched to subcutaneous. Oral MTX to subcutaneous MTX: 6 months after switching, the ACR score (not specified) remained unchanged (p=0.89) with improvements in 12 (37.5%) patients.
Ravelli 1998	Prospective observational	6 months	256 patients with juvenile chronic arthritis (35% polyarticular)	MTX (127 oral, 129 intramuscular) Dose: 10 mg/m^2/week	At 6 months, response rate (≥50% reduction vs. baseline in the number of joints with active arthritis and/or the articular severity score) was similar (58% oral, 61% intramuscular). No significant differences were reported for adverse events (42% oral, 39% intramuscular).

CI: Confidence Interval; MISS: Methotrexate Intolerance Severity Score; OR: Odds Ratio

References

1. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

2. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum. 2012;64(6):2012-2021.

3. Klein A, Kaul I, Foeldvari I, Ganser G, Urban A, Horneff G. Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children With Juvenile Idiopathic Arthritis: An Observational Study With Patients From the German Methotrexate Registry. Arthritis Care Res. 2012;64(9):1349-1356.

4. Bulatovic M, Heijstek M, Verkaaik M, van Dijkhuizen E, Armbrust W, Hoppenreijs E, et al. High Prevalence of Methotrexate Intolerance in Juvenile Idiopathic Arthritis. Arthritis Rheum. 2011;63(7):2007-2013.

5. Franova J, Fingerhutova S, Kobrova K, Srp R, Nemcova D, Hoza J, et al. Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. Pediatr Rheumatol. 2016;14(1):11p

6. van Dijkhuizen E, Pouw J, Scheuern A, Hugle B, Hardt S, Ganser G, et al. Methotrexate intolerance in oral and subcutaneous administration in patients with juvenile idiopathic arthritis: a cross sectional, observational study. Clin Exp Rheumatol. 2016;34(1):148-54.

7. Zuber Z, Turowska-Heydel D, Sobczyk M, Banach-Gornicka M, Rusnak K, Piszczek A, et al. Methotrexate efficacy and tolerability after switching from oral to subcutaneous route of administration in juveline idiopathic arthritis. Reumatologia. 2016;54(1):19-23

8. Ravelli A, Gerloni V, Corona F, Falcini F, Lepore L, De Sanctis R, et al. for the Italian Pediatric Rheumatology Study Group. Oral versus intramuscular methotrexate in juvenile chronic arthritis. Clin Exp Rheumatol. 1998;16(2):181-3.

PICO 2: In children and adolescents with JIA and polyarthritis, should methotrexate or leflunomide be recommended?

Summary**:** The literature searches identified two RCTs that directly or indirectly addressed the question of whether methotrexate or leflunomide be recommended to patients with polyarticular JIA. Silverman et al.[1] performed a direct drug comparison of methotrexate (0.5 mg/kg/week, maximum 25 mg per week) and leflunomide (Table 1). The authors found that after 16 weeks there was a significant improvement in the ACR Pedi 30 response in the methotrexate group compared to the leflunomide group. The ACR Pedi 50 and 70 responses were not significantly different. Neither was the percent improvement index. There was also no significant difference noted in the number of active joints, limitations in ROM, physical/patient global assessments, CHAQ, and ESR between methotrexate and leflunomide groups at week 16. Findings were largely imprecise. This study is indirect in that it did not sub-analyze the polyarticular JIA population; instead, all types of JIA (pauciarticular, polyarticular and systemic) were analyzed together. Furthermore, the study was sponsored by the drug company Sanofi-Aventis, the manufacturer of both leflunomide and methotrexate. However, it is unclear whether publication bias may have affected this evidence base.

Giannini et al.[2] compared methotrexate PO to placebo (Table 2). It found significant differences between the number of joints with pain on motion (p= 0.016) and the number of joints with limited ROM (p= 0.04) in MTX (10 mg per square meter of body surface per week) vs. placebo. However, it suffered from substantial indirectness in that it did not specifically analyze polyarticular JIA patients and also did not include the drug leflunomide in its comparisons. The criteria for enrollment was also vague in that the patients from the U.S. had to meet the ACR guidelines for a diagnosis of JRA, however patients from Europe were diagnosed based on unpublished criteria denoted as "criteria used in the Soviet Union and Eastern Europe." The outcome measurements used in this study were also inconsistent compared to other studies.

Overall quality of evidence across all critical outcomes: Moderate (based on direct evidence)

Table 1. Leflunomide compared to Methotrexate for polyarticular JIA

Bibliography: Silverman E et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. The New England journal of medicine 2005; 352(16): 1655-66.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With MTX	With Leflunomide		Risk with MTX	Risk difference with Leflunomide

Table 1. Leflunomide compared to Methotrexate for polyarticular JIA

Bibliography: Silverman E et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. The New England journal of medicine 2005; 352(16): 1655-66.

Quality assessment							Summary of findings				
ACR Pedi 30 Responses Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	not serious	none [b]	⊕⊕⊕⊕ HIGH	42/47 (89.4%)	32/47 (68.1%)	**RR 0.76** (0.61 to 0.95) **Favors MTX**	894 per 1,000	**214 fewer per 1,000** (349 fewer to 45 fewer)
ACR Pedi 50 Responses Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	36/47 (76.6%)	28/47 (59.6%)	**RR 0.78** (0.59 to 1.03)	766 per 1,000	**169 fewer per 1,000** (314 fewer to 23 more)
ACR Pedi 70 Responses Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	28/47 (59.6%)	20/47 (42.6%)	**RR 0.71** (0.48 to 1.07)	596 per 1,000	**173 fewer per 1,000** (310 fewer to 42 more)
Percent Improvement Index Pooled Week 16											

Table 1. Leflunomide compared to Methotrexate for polyarticular JIA

Bibliography: Silverman E et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. The New England journal of medicine 2005; 352(16): 1655-66.

Quality assessment							Summary of findings				
94 (1 RCT)	not serious	not serious [a]	not serious	serious [d]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **8.46 higher** (3.89 lower to 20.81 higher)
Number of Active Joints Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **0.8 higher** (1.97 lower to 3.57 higher)
Number of joints with limited ROM week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **0.1 higher** (2.12 lower to 2.32 higher)
Physician's Global Assessment Week 16											

Table 1. Leflunomide compared to Methotrexate for polyarticular JIA

Bibliography: Silverman E et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. The New England journal of medicine 2005; 352(16): 1655-66.

Quality assessment							Summary of findings				
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c,d]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **0.6 higher** (7.58 lower to 8.78 higher)
Patient Global Assessment Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **6.1 higher** (2.08 lower to 14.28 higher)
CHAQ Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **0.05 lower** (0.3 lower to 0.2 higher)
ESR Week 16											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	47	47	-	-	MD **0.7 higher** (2.77 lower to 4.17 higher)

Table 1. Leflunomide compared to Methotrexate for polyarticular JIA

Bibliography: Silverman E et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. The New England journal of medicine 2005; 352(16): 1655-66.

Quality assessment							Summary of findings				
ACR Pedi 30 Response Week 48											
68 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	32/35 (91.4%)	26/33 (78.8%)	**RR 0.86** (0.70 to 1.06)	914 per 1,000	**128 fewer per 1,000** (274 fewer to 55 more)
ACR Pedi 50 Responses Week 48											
68 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	30/35 (85.7%)	25/33 (75.8%)	**RR 0.88** (0.70 to 1.12)	857 per 1,000	**103 fewer per 1,000** (257 fewer to 103 more)
ACR Pedi 70 Responses Week 48											
68 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none [b]	⊕⊕⊕◯ MODERATE	29/35 (82.9%)	23/33 (69.7%)	**RR 0.84** (0.64 to 1.10)	829 per 1,000	**133 fewer per 1,000** (298 fewer to 83 more)
Serious Treatment Related Adverse Events Week 48											
94 (1 RCT)	not serious	not serious [a]	not serious	serious [c,d]	none [b]	⊕⊕⊕◯ MODERATE	4/47 (8.5%)	4/47 (8.5%)	**RR 1.00** (0.27 to 3.76)	85 per 1,000	**0 fewer per 1,000** (62 fewer to 235 more)

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. not applicable

b. study sponsored by Sanofi-Aventis

c. 95% CI overlaps the line of no difference

d. low number of events

Table 2. Low-Dose Methotrexate compared to Placebo for health problem or population

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Low-Dose MTX**		**Risk with Placebo**	**Risk difference with Low-Dose MTX**
Change in Articular Severity Score (composite of joint swelling, pain, tenderness, limitation of range of motion)											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	39	38	-	-	SMD **0.11 lower** (0.55 lower to 0.34 higher)

Table 2. Low-Dose Methotrexate compared to Placebo for health problem or population

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
Change in number of joints with pain on ROM											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [e]	none	⊕◯◯◯ VERY LOW	39	38	**Favors low-dose MTX**	-	SMD **1.34 lower** (1.84 lower to 0.85 lower)
Change in number of joints with tenderness											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.29 lower** (0.74 lower to 0.16 higher)
Change in duration of morning stiffness											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.12 lower** (0.57 lower to 0.32 higher)
Change in number of joints with active arthritis											

Table 2. Low-Dose Methotrexate compared to Placebo for health problem or population

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.17 lower** (0.62 lower to 0.27 higher)
Change in number of joints with limitation of motion											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [e]	none	⊕◯◯◯ VERY LOW	39	38	**Favors low-dose MTX**	-	SMD **0.5 lower** (0.95 lower to 0.04 lower)
Change in number of joints with swelling											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.28 lower** (0.73 lower to 0.17 higher)

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. randomization not described, high dropout rate, subgroup analysis of JIA subtypes not performed

b. not applicable

c. study uses clinical indices to report patient outcomes that are not consistent with other studies, study uses all JIA patients pooled together and does not sub-analyze polyarticular JIA patients

d. single study, includes no difference (which in this case is 0)

e. single study

References

1. Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med. 2005;352(16):1655-1666.

2. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

PICO 3: In children and adolescents with JIA and polyarthritis, should methotrexate or sulfasalazine be recommended?

Summary: This PICO was addressed by indirect comparisons in three placebo-controlled RCTs,[1-3] and one retrospective observational study evaluating methotrexate.[4] Low-dose methotrexate was favored over placebo for two efficacy outcomse (change in number of joints with limitation of motion and number of joints with limited ROM) in one small RCT (n=77, Table 1).[1] The criteria for enrollment was vague in that the patients from the U.S. had to meet the ACR guidelines for a diagnosis of JRA, however patients from Europe were diagnosed based on unpublished criteria denoted as "criteria used in the Soviet Union and Eastern Europe."[1] Sulfasalazine was favored over placebo for the majority of efficacy outcomes (including ACR 30 and remission) in two RCTs enrolling 61 to 69 patients (Table 2).[2,3] The primary van Rossum trial was a 24-week trial conducted in 1998, while the 2007 van Rossum trial measured outcomes at a median of 9 years. Only 3 SAEs were reported in SSZ patients in the earlier trial.[2] Lastly, one retrospective observational study evaluating methotrexate in 123 polyarthritis patients indicated that longer duration of methotrexate (>4/≤ 4 years) was significantly associated with no inactive disease (OR 2.67; 95% CI: 1.08 to 6.62; p<0.05)(Table 3).[4]

Quality of evidence across all critical outcomes**:** Very low

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarticular JIA

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Low-Dose MTX		Risk with Placebo	Risk difference with Low-Dose MTX
Change in Articular Severity Score (composite of joint swelling, pain, tenderness, limitation of range of motion)											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarticular JIA

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	39	38	-	-	SMD **0.11 lower** (0.55 lower to 0.34 higher)
Change in number of joints with pain on ROM											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	39	38	**Favors low-dose MTX**	-	SMD **1.34 lower** (1.84 lower to 0.85 lower)
Change in number of joints with tenderness											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	39	38	-	-	SMD **0.29 lower** (0.74 lower to 0.16 higher)
Change in duration of morning stiffness											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarticular JIA

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.12 lower** (0.57 lower to 0.32 higher)
Change in number of joints with active arthritis											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.17 lower** (0.62 lower to 0.27 higher)
Change in number of joints with limitation of motion											
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⊕⊕◯◯ LOW	39	38	**Favors low-dose MTX**	-	SMD **0.5 lower** (0.95 lower to 0.04 lower)
Change in number of joints with swelling											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarticular JIA

Bibliography: Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. The New England journal of medicine 1992; 326(16): 1043-9.

Quality assessment							Summary of findings				
77 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	39	38	-	-	SMD **0.28 lower** (0.73 lower to 0.17 higher)

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. randomization not described, high dropout rate, no subgroup analysis of polyarticular JIA performed

b. not applicable

c. study uses measures to report clinical outcomes that are not consistent with other studies

d. single study, includes no difference (which in this case is 0)

Table 2. Sulfasalazine compared to Placebo for patients with polyarticular JIA

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With SSZ**		**Risk with placebo**	**Risk difference with SSZ**
ACR30, median 9yrs											

Table 2. Sulfasalazine compared to Placebo for patients with polyarticular JIA

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
61 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	5/29 (17.2%)	15/32 (46.9%)	**OR 4.24** (1.29 to 13.89) **Favors SSZ**	172 per 1,000	**297 more per 1,000** (39 more to 571 more)
Remission, median 9yrs											
61 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	1/29 (3.4%)	8/32 (25.0%)	**OR 9.33** (1.09 to 80.06) **Favors SSZ**	34 per 1,000	**215 more per 1,000** (3 more to 706 more)
Remission between primary study and f/u, median 9yrs											
61 (1 RCT)	not serious	not serious [a]	serious [b]	serious [g]	none	⊕⊕◯◯ LOW	4/29 (13.8%)	13/32 (40.6%)	**OR 4.28** (1.20 to 15.22) **Favors SSZ**	138 per 1,000	**269 more per 1,000** (23 more to 571 more)
At least 50% improvement, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	15/34 (44.1%)	23/35 (65.7%)	**OR 2.43** (0.92 to 6.42)	441 per 1,000	**216 more per 1,000** (20 fewer to 394 more)

Table 2. Sulfasalazine compared to Placebo for patients with polyarticular JIA

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
At least 30% improvement, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	7/34 (20.6%)	15/35 (42.9%)	**OR 2.89** (0.99 to 8.41)	206 per 1,000	**222 more per 1,000** (2 fewer to 480 more)
Number of joints with limitation of motion, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	34	35	-	-	MD **0.52 lower** (3.22 lower to 2.18 higher)
Number of active joints, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⊕⊕◯◯ LOW	34	35	**Favors SSZ**	-	MD **4.76 lower** (8.06 lower to 1.46 lower)
Patients' score of disease activity, 24w											

Table 2. Sulfasalazine compared to Placebo for patients with polyarticular JIA

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	34	35	**Favors SSZ**	-	MD **0.68 lower** (1.18 lower to 0.18 lower)
Parents' score of disease activity, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	34	35	**Favors SSZ**	-	MD **0.54 lower** (0.96 lower to 0.12 lower)
Physicians' score of disease activity, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	34	35	**Favors SSZ**	-	MD **0.96 lower** (1.47 lower to 0.45 lower)
ESR, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	34	35	**Favors SSZ**	-	MD **0.7 lower** (0.91 lower to 0.49 lower)

Table 2. Sulfasalazine compared to Placebo for patients with polyarticular JIA

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
CRP, 24w											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	34	35	**Favors SSZ**	-	MD **0.44 lower** (0.83 lower to 0.05 lower)
Toxic reaction with anorexia											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**
Cervical lymphadenopathy											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**
Increased liver transaminase levels (3x over baseline)											
69 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison (SSZ vs. placebo)

c. Small single study. 95% CI includes the line of no difference.

d. Small single study

e. Small single study with only 1 event

f. Small single study. Very wide CI.

g. Small single study. Wide CI.

Table 3. Studies with Additional Relevant Data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
410, van Rossum, 2007	RCT	Median 9 years	61 patients with polyarticular JIA	SSZ: n=32 Placebo: n=29	Median (IQR) scores for active joints were lower for SSZ vs placebo (2 [0 to 3] SSZ, 4 [1 to 7] placebo; p<0.05)
					Median (IQR) scores for limited joints were lower for SSZ vs placebo (4 [1 to 12] SSZ, 7 [3 to 13] placebo; p value not reported)
					Median (IQR) scores for Physician Global Assessment of Disease Activity were lower for SSZ vs placebo (1.5 [0 to 2] SSZ, 2 [1 to 3] placebo; p value not reported)
					Median (IQR) scores for ESR were lower for SSZ vs placebo (6 [4 to 18] SSZ, 10 [7 to 26] placebo; p value not reported).
					Median (IQR) scores for CHAQ were similar (0.25 [0 to 1.8) SSZ, 0.25 [0 to 2] placebo; p value not reported)
					Significantly more SSZ patients achieved ACR30 vs placebo (47% SSZ vs. 17% placebo; p<0.05)
					Significantly more SSZ patients achieved remission vs placebo (25% SSZ vs. 3% placebo; p<0.05).
					Significantly more SSZ patients had episodes of remission between primary SSZ trial and followup trial vs placebo (41% SSZ vs. 14% placebo; p<0.05)
363, Magnani, 2009 [5]	Retrospective cohort	Nov 1986-Feb 2002	123 patients with polyarticular JIA	Methotrexate (dose and duration of treatment not defined)	Longer duration of MTX (>4/≤ 4 years) significantly associated with no inactive disease (OR 2.67, 95% CI: 1.08 to 6.62; p<0.05)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Disease inactivity defined as (active joint count = 0, physicians global, absence of systemic symptoms, no uveitis, negative acute phase reactants.	

References:

1. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.
2. van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
3. van Rossum MA, van Soesbergen RM, Boers M, Zwinderman AH, Fiselier TJ, Franssen MJ, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.
4. Magnani A, Pistorio A, Magni-Manzoni S, Falcone A, Lombardini G, Bandeira M, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. J Rheumatol. 2009;36(3):628-634.

PICO 4. In children and adolescents with JIA and polyarthritis and LDA (risk factor irrespective), should adding a limited course of prednisone (e.g. bridging/dosing TBD) to initial therapy versus not adding prednisone be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 5. In children and adolescents with JIA and polyarthritis and moderate/ HDA (risk factor irrespective), should adding a limited course of prednisone (e.g., bridging/dosing TBD) to initial therapy versus not adding prednisone be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 6. In children and adolescents with JIA and polyarthritis and LDA (risk factor irrespective) with initial non-biologic DMARD therapy, should treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus adding a biologic be recommended?

Summary: This PICO was addressed by one RCT in a direct drug comparison.[1] Results show statistically significant differences in JIA ACR 70 and JIA ACR 90 favoring tocilizumab, and no between-group difference in serious adverse events.

Quality of evidence across all critical outcomes: Low

Tocilizumab (8mg/kg or 10mg/kg) compared to Glucocorticoid for health problem or population [1]

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Glucocorticoid	With Tocilizumab (8mg/kg or 10mg/kg)		Risk with Glucocorticoid	Risk difference with Tocilizumab (8mg/kg or 10mg/kg)
JIA ACR 70											
87 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	14/38 (36.8%)	30/49 (61.2%)	**OR 2.71** (1.13 to 6.49) **Favors Tocilizumab**	368 per 1,000	**244 more per 1,000** (29 more to 423 more)
JIA ACR 90											
87 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	5/38 (13.2%)	21/49 (42.9%)	**OR 4.95** (1.65 to 14.84) **Favors Tocilizumab**	132 per 1,000	**297 more per 1,000** (68 more to 561 more)

Tocilizumab (8mg/kg or 10mg/kg) compared to Glucocorticoid for health problem or population [1]

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
Serious Adverse Events											
163 (1 RCT)	not serious	not serious	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	3/81 (3.7%)	3/82 (3.7%)	**OR 0.99** (0.19 to 5.04)	37 per 1,000	**0 fewer per 1,000** (30 fewer to 125 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Randomization, allocation, blinding, and outcome reporting not mentioned

b. Compares patients on tocilizumab to patients on placebo, methotrexate, and glucocorticoids

c. Wide 95% CI crosses the no effect line

References

1. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

PICO 7. In children and adolescents with JIA and polyarthritis and LDA (risk factor irrespective) with biologic therapy (+/- non-biologic DMARD), should adding treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus switching biologic be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 8. In children and adolescents with JIA and polyarthritis and moderate/HDA (risk factor irrespective) with biologic therapy (+/- non biologic DMARD), should adding treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus switching biologic be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 9. In children and adolescents with JIA and polyarthritis and active disease (risk factor and current/prior treatment irrespective), should treatment with intraarticular glucocorticoids versus no treatment with intraarticular glucocorticoids be recommended?

Summary: This PICO question was addressed directly by one observational study.[1] This retrospective cohort study examined multiple intraarticular corticosteroid injections in 220 patients with polyarticular JIA. 61% percent of patients were administered injections in 3 or 4 joints while 39% were administered injections in ≥5 joints, and 57% of patients were on ongoing or newly started methotrexate. A statistically significant difference was reported in injected joints with sustained remission vs. synovitis flares; however, 66% of patients experienced a flare shortly after (median 0.5 years). This discrepancy occurred because most patients with a flare had injections in multiple joints, and flare occurred in less than half of the injected joints. The risk of flare was significantly lower among patients receiving methotrexate (see Results in table below).

Overall quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
196, Papadopoulou, 2012	Cohort	Minimum of 6 months post-injection	220 patients with polyarticular JIA, 1096 joints injected (1079 joints where outcome was assessed). First of multiple IAC injections (simultaneous injection of ≥ 3 joints) were received between 2002 and 2011	Triamcinolone hexacetonide for large joints and methylprednisolone acetate for small or difficult joints	Statistically significant difference in injected joints with sustained remission versus synovitis flares (71.4% vs. 28.6%; p< 0.0001). However, 146/220 patients (66.4%) experienced a flare after a median of 0.5 years. Significantly fewer patients receiving methotrexate experienced a flare (58.8%) compared to patients not receiving methotrexate (76.8%)(p = 0.022). Lack of methotrexate use was also significantly associated with flare in a Cox regression model (Hazard ratio 1.91, 95% CI 1.30-2.81).

References

1. Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, Bohm M, Nieto-Gonzalez JC, Pistorio A, et al. Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken). 2013;65(7):1112-1120.

PICO 10. In children and adolescents with JIA and polyarthritis, should treatment with intraarticular triamcinolone acetonide versus triamcinolone hexacetonide be recommended?

Summary: One RCT[1], downgraded by one level for indirectness by type of JIA (most patients had persistent oligoarticular), addressed this question. It compared the efficacy of intraarticular triamcinolone acetonide (TA) with triamcinolone hexacetonide (TH) as measured by sustained response and joint remission at 6, 12, and 24 months follow-up; skin atrophy was reported as an adverse event. All efficacy outcomes significantly favored TH use. The result for skin atrophy showed no significant difference between drugs, but the finding was imprecise due to the low number of events.

Quality of Evidence: Moderate

Triamcinolone acetonide compared to Triamcinolone hexacetonide for Intraarticular treatment of symmetrical joints in JIA

Bibliography: Zulian, F., et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004; 43(10), 1288-1291.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Triam-cinolone hexacetonide	With Triam-cinolone acetonide		Risk with Triam-cinolone hexacetonide	Risk difference with Triam-cinolone acetonide
Sustained response 6 months											
78 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	35/39 (89.7%)	24/39 (61.5%)	**OR 0.18** (0.05 to 0.62) **Favors TH**	897 per 1,000	**286 fewer per 1,000** (593 fewer to 53 fewer)
Sustained response 12 months											

Triamcinolone acetonide compared to Triamcinolone hexacetonide for Intraarticular treatment of symmetrical joints in JIA

Bibliography: Zulian, F., et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004; 43(10), 1288-1291.

Quality assessment							Summary of findings				
78 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	33/39 (84.6%)	19/39 (48.7%)	**OR 0.17** (0.06 to 0.50) **Favors TH**	846 per 1,000	**363 fewer per 1,000** (598 fewer to 113 fewer)
Sustained response 24 months											
78 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	30/39 (76.9%)	15/39 (38.5%)	**OR 0.19** (0.07 to 0.50) **Favors TH**	769 per 1,000	**381 fewer per 1,000** (580 fewer to 144 fewer)
Joint remission 12 months											
78 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	31/39 (79.5%)	19/39 (48.7%)	**OR 0.25** (0.09 to 0.67) **Favors TH**	795 per 1,000	**303 fewer per 1,000** (536 fewer to 73 fewer)
Joint remission 24 months											

Triamcinolone acetonide compared to Triamcinolone hexacetonide for Intraarticular treatment of symmetrical joints in JIA

Bibliography: Zulian, F., et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004; 43(10), 1288-1291.

Quality assessment							Summary of findings				
78 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	25/39 (64.1%)	13/39 (33.3%)	**OR 0.28** (0.11 to 0.71) **Favors TH**	641 per 1,000	**308 fewer per 1,000** (477 fewer to 82 fewer)
Adverse events - skin atrophy											
78 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	1/39 (2.6%)	1/39 (2.6%)	**OR 1.00** (0.06 to 16.58)	26 per 1,000	**0 fewer per 1,000** (24 fewer to 278 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Most patients have Persistent Oligoarticular subtype of JIA
b. Wide 95% CI crosses line of no difference

References

1. Zulian, F., Martini, G., Gobber, D., Plebani, M., Zacchello, F., & Manners, P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004; 43(10), 1288-1291.

PICO 11: In children and adolescents with JIA and polyarthritis, should etanercept monotherapy versus etanercept + non-biologic DMARD be recommended?

Summary: This PICO was addressed by one placebo-controlled RCT (indirect comparison),[1] and two observational study direct drug comparisons.[2,3] Evidence was supplemented by five observational studies[4-6, 9,10] and one open-label extended treatment trial.[7,8]

Two studies reported on etanercept monotherapy vs. etanercept plus methotrexate (Table 1). [2,3] Horneff reported significant differences favoring etanercept plus methotrexate vs. etanercept for ACR 70 at 12 months; ACR 30/50 were borderline significant.[3] One study reported statistically significantly more autoimmune events and exposure-adjusted rates of SAEs per 100 patient-years were higher with etanercept monotherapy,[2] while the other study reported non-significant but higher rates of infectious and non-infectious SAEs with combination treatment.[3]

Results from one RCT comparing etanercept with placebo in methotrexate-resistant JIA patients indicated a statistically significant difference favoring etanercept in 30% improvement over baseline at 7 months, but no significant difference in active joint count or joints with limitation of motion (Table 2). Depression/personality disorder and gastroenteritis-flu syndrome occurred in one etanercept patient each. Two patients tested positive for non-neutralizing antibody to etanercept.[1] Additional evidence from Lovell is provided in the open-label extended treatment trial. Two years into this trial, 69% of the 51 patients (intent-to-treat group) met the juvenile rheumatoid arthritis (JRA) 30, 67% met the JRA 50, and 57% met the JRA 70. One patient who was taking etanercept for more than 2 years had sepsis.[7] Eight years into this trial, ACR pedi 30/50/70/90/100 response rates were 83%/77%/61%/41%/18%, respectively, and the overall SAE rate remained at 0.12 events/patient-year.[8]

Additional evidence from observational studies for etanercept includes a much higher incidence of an IBD event with etanercept monotherapy vs. etanercept plus methotrexate (5.33 vs. 0.62 per 1000 patient years),[5] and an infection rate per 100 patient years of 1.43 with etanercept monotherapy (1.30 to 1.97)(Table 3).[4] Another study found no significant between-group difference in rates of medically significant infections and serious infections for etanercept monotherapy vs. etanercept plus methotrexate.[9]

Additional evidence from observational studies for non-biologic DMARDs includes a significantly higher incidence of IBD in patients exposed to sulfasalazine (OR 9.34, 95% CI: 2.05 to 43.51; $p<0.05$), but significantly lower incidence of IBD in patients exposed to methotrexate (OR 0.12, 95% CI: 0.03 to 0.55; $p<0.05$). Leflunomide was not significantly associated with incidence of IBD (OR 3.86, 95% CI: 0.49 to 30.27; NS).[5] Lastly, concomitant methotrexate was not associated with a greater chance of remission on medication (OR 0.91; $p=0.7$), and was borderline significantly associated with an increased chance of inactive disease (OR 1.39; $p=0.051$)(Table 3).[6]

Quality of evidence across all critical outcomes: Very low

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Etanercept plus MTX	**With Etanercept**		**Risk with Etanercept plus MTX**	**Risk difference with Etanercept**
Physician's global assessment of 0, 36 mos (3-36 mos data available)											
157 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	35/115 (30.4%)	17/42 (40.5%)	**OR 1.55** (0.75 to 3.24)	304 per 1,000	**100 more per 1,000** (57 fewer to 282 more)
Total active joint score of 0, 36 mos (3-36 mos data available)											
157 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	58/115 (50.4%)	24/42 (57.1%)	**OR 1.31** (0.64 to 2.67)	504 per 1,000	**67 more per 1,000** (110 fewer to 227 more)
Number of active joints, 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **0.4 lower** (1.51 lower to 0.71 higher)

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
Number of joints with limited mobility, 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **0.4 lower** (2.27 lower to 1.47 higher)
Patient's assessment (100 mm VAS), 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **0.3 higher** (0.24 lower to 0.84 higher)
Doctor's assessment (100 mm VAS), 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **0.2 higher** (0.4 lower to 0.8 higher)
CHAQ, 12 mos											

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **0.06 lower** (0.19 lower to 0.07 higher)
ESR (mm/h), 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [e]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **4 lower** (7.05 lower to 0.95 lower)
CRP (mg/litre), 12 mos											
431 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [f]	none	⊕◯◯◯ VERY LOW	376	55	-	-	MD **2 higher** (10.26 lower to 14.26 higher)
ACR30, 12 mos											
486 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [e]	none	⊕◯◯◯ VERY LOW	338/419 (80.7%)	47/67 (70.1%)	**OR 0.56** (0.32 to 1.00)	807 per 1,000	**106 fewer per 1,000** (235 fewer to 0 fewer)

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
ACR50, 12 mos											
486 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	310/419 (74.0%)	42/67 (62.7%)	**OR 0.59** (0.34 to 1.01)	740 per 1,000	**113 fewer per 1,000** (248 fewer to 2 more)
ACR70, 12 mos											
486 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [e]	none	⊕◯◯◯ VERY LOW	261/419 (62.3%)	30/67 (44.8%)	**OR 0.49** (0.29 to 0.83) **Favors ETN + MTX**	623 per 1,000	**176 fewer per 1,000** (299 fewer to 45 fewer)
Infectious SAE, 12 mos											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	25/504 (5.0%)	1/100 (1.0%)	**OR 0.19** (0.03 to 1.45)	50 per 1,000	**40 fewer per 1,000** (48 fewer to 21 more)
Non-infectious SAE, 12 mos											

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	23/504 (4.6%)	3/100 (3.0%)	**OR 0.65** (0.19 to 2.20)	46 per 1,000	**15 fewer per 1,000** (37 fewer to 50 more)
Total medically important infections (per 100 patient years)											
397 (1 observational study) Horneff	serious [a]	not serious [b]	not serious	serious [c]	none	⊕◯◯◯ VERY LOW	13/294 (4.4%)	4/103 (3.9%)	**OR 0.87** (0.28 to 2.74)	44 per 1,000	**6 fewer per 1,000** (31 fewer to 68 more)
Thyroid carcinoma											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)
Yolk sac carcinoma											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
Non-Hodgkin's lymphoma											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)
Stevens-Johnson syndrome											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)
Crohn's disease											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)
Pyelonephritis											

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [h]	none	⊕◯◯◯ VERY LOW	2/294 (0.7%)	0/103 (0.0%)	**OR 0.57** (0.03 to 11.87)	7 per 1,000	**3 fewer per 1,000** (7 fewer to 68 more)
Abscess											
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [h]	none	⊕◯◯◯ VERY LOW	2/294 (0.7%)	0/103 (0.0%)	**OR 0.57** (0.03 to 11.87)	7 per 1,000	**3 fewer per 1,000** (7 fewer to 68 more)
Bronchitis											
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/294 (0.3%)	0/103 (0.0%)	**OR 0.95** (0.04 to 23.39)	3 per 1,000	**0 fewer per 1,000** (3 fewer to 71 more)
Urosepsis											
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/294 (0.3%)	0/103 (0.0%)	**OR 0.95** (0.04 to 23.39)	3 per 1,000	**0 fewer per 1,000** (3 fewer to 71 more)

Table 1. Etanercept compared to Etanercept plus MTX for polyarticular JIA

Bibliography: Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804. Horneff G, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-525.

Quality assessment							Summary of findings				
Clostridium difficile colitis											
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/294 (0.3%)	0/103 (0.0%)	**OR 0.95** (0.04 to 23.39)	3 per 1,000	**0 fewer per 1,000** (3 fewer to 71 more)
Autoimmune events											
397 (1 observational study) Giannini	serious [a]	not serious [b]	not serious	serious [e]	none	⊕◯◯◯ VERY LOW	15/294 (5.1%)	12/103 (11.7%)	**OR 2.45** (1.11 to 5.43) **Favors ETN + MTX**	51 per 1,000	**65 more per 1,000** (5 more to 175 more)
Sepsis											
604 (1 observational study) Horneff	serious [d]	not serious [b]	not serious	serious [g]	none	⊕◯◯◯ VERY LOW	1/504 (0.2%)	0/100 (0.0%)	**OR 1.67** (0.07 to 41.29)	2 per 1,000	**1 more per 1,000** (2 fewer to 74 more)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Retrospective, non-randomized, no blinding

b. Not applicable

c. Single study. 95% CI includes the line of no difference.

d. Prospective, non-randomized, no blinding

e. Single study

f. Single study. Wide 95% CI that overlaps the line of no difference.

g. Single study with only 1 event. Very wide 95% CI that overlaps the line of no difference.

h. Single study with very few events. Very wide 95% CI that overlaps the line of no difference.

Table 2. Etanercept compared to placebo for polyarticular JIA

Bibliography: Lovell DJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Etanercept**		**Risk with placebo**	**Risk difference with Etanercept**
Active joint count (median), 7 mos											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	13/26 (50.0%)	7/25 (28.0%)	**OR 0.39** (0.12 to 1.24)	500 per 1,000	**219 fewer per 1,000** (393 fewer to 54 more)
Joints with limitation of motion (median), 7 mos											

Table 2. Etanercept compared to placebo for polyarticular JIA

Bibliography: Lovell DJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.

Quality assessment							Summary of findings				
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	5/26 (19.2%)	1/25 (4.0%)	**OR 0.17** (0.02 to 1.62)	192 per 1,000	**153 fewer per 1,000** (188 fewer to 86 more)
Improvement (30% over baseline), 7 mos											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/26 (34.6%)	20/25 (80.0%)	**OR 7.56** (2.12 to 26.91)	346 per 1,000	**454 more per 1,000** (183 more to 588 more)
Depression / personality disorder											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/26 (0.0%)	1/25 (4.0%)	**OR 3.24** (0.13 to 83.47)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Gastroenteritis-flu syndrome											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/26 (0.0%)	1/25 (4.0%)	**OR 3.24** (0.13 to 83.47)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
HACA formation (Antibodies to Etanercept)											

Table 2. Etanercept compared to placebo for polyarticular JIA

Bibliography: Lovell DJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.

Quality assessment							Summary of findings				
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [f]	none	⨁⨁◯◯ LOW	0/26 (0.0%)	2/25 (8.0%)	**OR 5.64** (0.26 to 123.51)	0 per 1,000	**Not calculable**

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison

c. Small single study, 95% CI includes the line of no difference.

d. Small single study.

e. Small single study with only 1 event. Very wide 95% CI overlaps the line of no difference.

f. Small single study with very few events. Very wide 95% CI overlaps the line of no difference.

Table 3. Additional Evidence from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Beukelman, 2016[4]	Retrospective observational study	10 years	3075 MTX and 2713 TNFi patients	MTX, TNFi's	The infection rate per 100 py for MTX was 1.46 (1.07-2.00), for all TNFi monotherapy was 1.54 (1.09-2.17), for TNFi+MTX was 1.74 (1.11-2.72); for individual TNFi's the infection rate for Etanercept was 1.43 (1.03-1.97), Adalimumab 2.90 (1.65-5.11), Infliximab 1.32 (0.43-4.10).
Barthel, 2015[5]	Cohort study	2001-2013 (German biologics registry)	3071 patients with JIA; 11 patients diagnosed with inflammatory bowel disease (IBD)	Etanercept Methotrexate Sulfasalazine	Incidence of an IBD event was much higher in Etanercept monotherapy vs Etanercept plus MTX (5.33 vs. 0.62 per 1000 patient years). Incidence of IBD was significantly higher in patients exposed to Etanercept (OR 6.11, 95% CI: 1.32 to 28.32; p<0.05) and Sulfasalazine (OR 9.34, 95% CI: 2.05 to 43.51; p<0.05), but significantly lower in

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Leflunomide	patients exposed to Methotrexate (OR 0.12, 95% CI: 0.03 to 0.55; p<0.05). Leflunomide was not significantly associated with incidence of IBD (OR 3.86, 95% CI: 0.49 to 30.27; NS).
290, Papsdorf and Horneff, 2011	Cohort study	NR	787 patients with polyarticular JIA	MTX: 567 No MTX: 220	Concomitant MTX was borderline significantly associated with an increased chance of inactive disease (OR 1.39; p=0.051). Concomitant MTX was not associated with a greater chance of remission on medication (OR 0.91; p=0.7).
Giannini, 2009[2]	Cohort study	3 years	397 patients with polyarticular JIA	Etanercept: 103 Etanercept plus MTX: 294	Exposure-adjusted rates of serious adverse events per 100 patient-years were higher in Etanercept mono (7.1 Etanercept, 6.0 Etanercept plus MTX).
Lovell, 2003[7], 2008[8]	Open-label, extended-treatment trial (primary trial, Lovell 2000[1])	2 years, 8 years	43 MTX-resistant JIA patients at 2 years, 51 MTX-resistant JIA patients in modified ITT 26 patients at 8 years	Etanercept was administered at a dosage of 0.4 mg/kg (maximum 25 mg) subcutaneously twice each week	Two years into this extension trial, 69% of the 51 patients (ITT group) met the JRA 30, 67% met the JRA 50, and 57% met the JRA 70. 1 patient who was taking ETN for more than 2 years had SAE (sepsis). 8 years into the extension trial, the overall SAE rate remained at 0.12 events/patient-year. ITT analysis found ACR pedi 30/50/70/90/100 response rates of 83%/77%/61%/41%/18%.
7153, Davies, 2015[9]	Cohort Study	2.6 years for ETN, 3 for MTX	852 ETN-treated and 260MTX-treated JIA patients	Etanercept, ETN+MTX, MTX	The most common medically significant infections (MSIs) were varicella and respiratory tract infections. The ETN-treated patients showed an increase in the rate of MSIs, with a crude incidence rate of 5.5 per 100 person-years (95% CI 4.5–6.6) versus 3.4 per 100 person-years (95% CI 2.2–5.0) for MTX. Within the ETN cohort, patients receiving monotherapy had an incidence rate of 4.3 per 100 person-years (95% CI 3.2–5.7), as compared to 7.2 per 100 person-years (95% CI 5.4–9.3) in the ETN plus MTX cohort. The unadjusted hazard ratio (HR) for the ETN + MTX -treated patients versus the ETN-treated patients was 1.47 (95% CI 0.99–2.17). A fully adjusted hazard ratio was 1.42 (95% CI 0.89–2.25), which did not differ significantly between groups, but the wide 95% CI means that a between-group difference cannot be ruled out.. The unadjusted HR for Serious Infections in the ETN + MTX-treated patients versus the ETN-treated patients was 1.23 (95% CI 0.66–2.29). The fully adjusted HR showed a similar result, with an HR of 1.29 (95% CI 0.63–2.62).

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
110, Klotsche, 2016[10]	Prospective cohort study	11 years	1162 patients with ETA, 46 with ADA, 1055 biologic-naive MTX. 40% Poly-JIA, 7.6% systemic JIA, 50% with extra-articular manifestations	ETN, ADA, MTX	75 SAEs (2.6 events/100 EY) under MTX, 199 SAEs (4.5 events/100 EY, relative risk (RR)=2.2, p<0.001) under ETA and 23 (4.7 events/100 EY, RR=2.2, p=0.006) under ADA treatment. 41 medically important infections were recorded in the ETA group (0.9 events/100 EY, RR=2.1, p=0.03), 2 in the ADA group (0.4 events/100EY, RR=0.8, p=0.87) and 15 in the MTX group (0.5 events/100 EY). The rate of MII was increased for ETA with concomitant MTX use (1.03 events/100 EY) versus ETA monotherapy (0.7 events/100 EY). Similar rates for sepsis were seen for MTX (0.03 events/100 EY) and ETA (0.07 events/100 EY, p=0.540).

References

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2. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804.
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10. Klotsche J, Niewerth M, Haas JP, Huppertz HI, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.

PICO 12. In children and adolescents with JIA and polyarthritis, should adalimumab monotherapy versus adalimumab + non-biologic DMARD be recommended?

Summary: This PICO was addressed by direct drug comparison in one RCT[1] (Table 1) and indirect comparison in one observational study[2] (Table 2). The results show no significant differences in JIA ACR 30, 50, 70, 90, and SAE. Significantly more adalimumab monotherapy patients (versus adalimumab plus methotrexate patients) had at least one positive test for anti-adalimumab antibody through 48 weeks (25.6% vs. 5.9%). Authors noted that the development of anti-adalimumab antibody was not associated with higher rates of discontinuation of study drug or SAE incidence.[1]

Overall quality of evidence across all critical outcomes: Moderate

Table 1. Adalimumab monotherapy compared to Adalimumab + MTX for health problem or population

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Adalimumab monotherapy	**With Adalimumab + MTX**		**Risk with Adalimumab monotherapy**	**Risk difference with Adalimumab + MTX**
ACR 30											
68 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	17/30 (56.7%)	24/38 (63.2%)	**RR 1.11** (0.75 to 1.66)	567 per 1,000	**62 more per 1,000** (142 fewer to 374 more)
ACR 50											
68 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	16/30 (53.3%)	24/38 (63.2%)	**RR 1.18** (0.78 to 1.79)	533 per 1,000	**96 more per 1,000** (117 fewer to 421 more)
ACR 70											

Table 1. Adalimumab monotherapy compared to Adalimumab + MTX for health problem or population

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Quality assessment							Summary of findings				
68 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	14/30 (46.7%)	24/38 (63.2%)	**RR 1.35** (0.86 to 2.13)	467 per 1,000	**163 more per 1,000** (65 fewer to 528 more)
ACR 90											
68 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	9/30 (30.0%)	16/38 (42.1%)	**RR 1.40** (0.72 to 2.72)	300 per 1,000	**120 more per 1,000** (84 fewer to 516 more)
SAE											
68 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	0/38 (0.0%)	0/30 (0.0%)	not estimable	0 per 1,000	**not estimable**
HACA formation (At least 1 positive test for anti-adalimumab antibody)											
171 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	22/86 (25.6%)	5/85 (5.9%)	**RR 0.23** (0.09 to 0.58) **Favors ADA plus MTX**	256 per 1,000	**197 fewer per 1,000** (233 fewer to 107 fewer)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Wide 95% CI crosses the no effect line.

Table 2. Observational Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2451, Beukelman, 2016 [2]	Retrospective observational study	10 years	3075 MTX and 2713 TNFi patients	MTX, TNFi's	The infection rate per 100 py for MTX was 1.46 (1.07-2.00), for all TNFi monotherapy was 1.54 (1.09-2.17), for TNFi+MTX was 1.74 (1.11-2.72); for individual TNFi's the infection rate for Etanercept was 1.43 (1.03-1.97), Adalimumab 2.90 (1.65-5.11), Infliximab 1.32 (0.43-4.10).

References

1. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.
2. Beukelman T, Xie F, Baddley JW, Chen L, Mannion ML, Saag KG, et al. The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis. Arthritis Res Ther. 2016;18(1):210.

PICO 13: In children and adolescents with JIA and polyarthritis, should infliximab monotherapy or infliximab + non-biologic DMARD be recommended?

Summary: The literature searches identified three studies that addressed this question, one RCT, an open-label extension of the RCT, and one retrospective cohort. The RCT by Ruperto[1] evaluated the efficacy and safety of infliximab in patients with polyarticular JIA. This trial did not specifically use the comparisons delineated in the PICO question, but instead looked at infliximab plus MTX vs. MTX alone as well as 2 different doses of infliximab. The authors found that in comparing infliximab plus MTX to MTX alone that while there were higher gross numbers of patients in the infliximab group that showed ACR Pedi 30/50/70 responses by week 14, the difference was not statistically significant (Table 1). There was a significant difference however, in the number of active joints (p=0.016), though no other significant differences in the core set variables at week 14. In looking at different doses of infliximab (6 mg/kg vs. 3 mg/kg) (Table 2), there also were no significant differences in the ACR Pedi 30/50/70 or active joint counts at week 52. Significant differences favoring 6 mg/kg dose were reported for serious adverse events and incidence of antibodies to infliximab at 64 weeks (12.2% vs. 37.7%). Authors noted that when compared with patients testing negative for antibodies to infliximab or patients with inconclusive test results, patients who tested positive for antibodies to infliximab had a 3-fold higher incidence of infusion reactions (58% positive, 19% negative, 12% inconclusive) and higher incidence of serious infusion reactions (20% vs. 0%).[1]A long-term open-label extension (all continuing patients received infliximab plus MTX) of this study found that at 204 weeks, the rates of ACR Pedi-30/50/70/90 responses were 44%/40%/33%/24% respectively, while 13% of patients had inactive disease; serious adverse events occurred in 22% of patients.[2]

The observational study by Beukelman[3] included 5788 patients in the total cohort (Table 3). This study mainly investigated TNFi compared to methotrexate in terms of hospitalized infections. Adjusted hazard ratios and infection rates per 100 patient years were used for comparison. They found that neither TNFi alone nor TNFi plus MTX were associated with increased risk of hospitalized infection compared to MTX alone. The findings of this study were indirect in that it is unclear the number of polyarticular JIA patients that were included in the cohort (though systemic JIA patients were analyzed separately). Furthermore, the sub-analysis of infliximab did not delineate the number of patients on infliximab and methotrexate vs. infliximab alone (the table compares MTX alone to infliximab as a whole).

Overall quality of evidence for all critical outcomes: Low

Table 1. Infliximab + MTX compared to MTX for health problem or population

Bibliography: Ruperto N, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. Infliximab + MTX compared to MTX for health problem or population

Bibliography: Ruperto N, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings				
(studies) Follow-up	bias					evidence	With MTX	With Infliximab + MTX	(95% CI)	Risk with MTX	Risk difference with Infliximab + MTX
ACR Pedi 30 14 weeks											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	29/62 (46.8%)	37/60 (61.7%)	**RR 1.32** (0.95 to 1.84)	468 per 1,000	**150 more per 1,000** (23 fewer to 393 more)
ACR Pedi 50 14 weeks											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	20/62 (32.3%)	29/60 (48.3%)	**RR 1.50** (0.96 to 2.34)	323 per 1,000	**161 more per 1,000** (13 fewer to 432 more)
ACR Pedi 70 14 weeks											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	7/62 (11.3%)	13/60 (21.7%)	**RR 1.92** (0.82 to 4.48)	113 per 1,000	**104 more per 1,000** (20 fewer to 393 more)

Table 1. Infliximab + MTX compared to MTX for health problem or population

Bibliography: Ruperto N, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings				
Serious adverse events (RCT)											
182 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	3/60 (5.0%)	24/122 (19.7%)	**RR 3.93** (1.23 to 12.55) **Favors MTX**	50 per 1,000	**147 more per 1,000** (12 more to 578 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. not applicable

b. treatment arms do not directly match PICO question

c. wide 95% confidence interval crosses no effect line

Table 2. Infliximab 3 mg + MTX compared to Infliximab 6 mg + MTX for health problem or population

Bibliography: Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings		
№ of participants	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of**	**Study event rates (%)**	**Relative effect**	**Anticipated absolute effects**

Table 2. Infliximab 3 mg + MTX compared to Infliximab 6 mg + MTX for health problem or population

Bibliography: Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings				
(studies) Follow-up	bias					evidence	With Infliximab 6 mg + MTX	With Infliximab 3 mg + MTX	(95% CI)	Risk with Infliximab 6 mg + MTX	Risk difference with Infliximab 3 mg + MTX
Number of patients with no active joints 52 weeks											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	26/60 (43.3%)	25/62 (40.3%)	**RR 0.93** (0.61 to 1.41)	433 per 1,000	**30 fewer per 1,000** (169 fewer to 178 more)
Serious adverse events											
117 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	5/57 (8.8%)	19/60 (31.7%)	**RR 3.61** (1.44 to 9.02) **Favors INF 6 mg + MTX**	88 per 1,000	**229 more per 1,000** (39 more to 704 more)
HACA formation (Antibodies to Infliximab), 64 weeks											

Table 2. Infliximab 3 mg + MTX compared to Infliximab 6 mg + MTX for health problem or population

Bibliography: Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9): 3096-106.

Quality assessment							Summary of findings				
102 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	6/49 (12.2%)	20/53 (37.7%)	**RR 3.08** (1.35 to 7.04) **Favors INF 6 mg + MTX**	122 per 1,000	**255 more per 1,000** (43 more to 740 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. not applicable

b. treatment arms do not match PICO question

c. wide 95% confidence interval crosses no effect line

Table 3. Infliximab vs. MTX; also TNFi vs. MTX

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2451, Beukelman T., 2016	Retrospective observational study	10 years	3075 MTX and 2713 TNFi patients	MTX, TNFi's	The infection rate per 100 py for MTX was 1.46 (1.07-2.00), for all TNFi monotherapy was 1.54 (1.09-2.17), for TNFi + MTX was 1.74 (1.11-2.72); for individual TNFi the infection rate for etanercept was 1.43 (1.03-1.97), adalimumab 2.90 (1.65-5.11), and infliximab 1.32 (0.43-4.10).

References

1. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007;56(9):3096-3106.

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3. Beukelman T, Xie F, Baddley JW, Chen L, Mannion ML, Saag KG, et al. The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis. Arthritis Res Ther. 2016;18(1):210.

PICO 14. In children and adolescents with JIA and polyarthritis, should golimumab monotherapy versus golimumab + non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 15. In children and adolescents with JIA and polyarthritis, should abatacept monotherapy versus abatacept + non-biologic DMARD be recommended?

Summary: Literature searches revealed three studies (2 RCTs and 1 open label extension) which seemed to indirectly address the PICO question (all patients had received prior DMARDs and most patients in both arms received concurrent methotrexate). Of the two RCTs, however, the data from one study[1] was not abstracted as both studies[1,2] included the same study population (both part of the AWAKEN trial). Ruperto 2008[2] included data from patients who dropped out in addition to those who remained in the study, while the other study[1] only analyzed those patients who remained in the study and thus was not a good representation of treatment efficacy. Ruperto[2] demonstrated that patients on abatacept significantly improved in terms of their number of active joints, number of joints with limited ROM, physician's global assessment, and CHAQ disability index compared to placebo (Table 1). The measurement for the disability index was imprecise, however, the remaining measurements remained significant. There was also a significantly higher number of patients in the abatacept group vs. placebo group who achieved an ACR Pedi 50/70/90 compared to controls. The difference in ACR Pedi 30 was not significant. There was no statistically significant difference in terms of serious adverse events between the groups. This study was an indirect representation of the PICO question as it compared abatacept to placebo (74% of patients were also receiving methotrexate in both groups) but not abatacept to a second DMARD. In addition, the study population included more than just polyarticular JIA patients. There was also no delineation between patients with risk factors and without which makes this indirect as the PICO question asked specifically about poly-JIA patients without risk factors.

An open-label extension study[3, 4] investigated improvement in patients from the initial AWAKEN trial over time (Table 2). As such, the same limitations about the indirectness of the population studied apply here. Researchers found that 19.6% of patients reported experiencing a serious adverse event by the end of the long-term extension period (up to 7 years). The majority of patients (85%) achieved an ACR 30, and 43% were found to achieve an ACR 90. However, these numbers dropped to 35% and 20.5% in an intention-to-treat analysis that assumed any dropouts or patients with missing data were non-responders. Authors concluded that patients on abatacept overall achieved clinically meaningful responses over the long-term.

Quality of evidence across all critical outcomes: Low

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
(studies) Follow-up	**bias**					**evidence**	**With Placebo end of 6 month period**	**With Abatacept**	**(95% CI)**	**Risk with Placebo end of 6 month period**	**Risk difference with Abatacept**
Number of joints with active arthritis											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⊕⊕⊕◯ MODERATE	62	60	**Favors abatacept**	-	MD **3.1 lower** (0.93 lower to 5.27 lower)
Physician Global Assessment of child's well being (VAS)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⊕⊕⊕◯ MODERATE	62	60	**Favors abatacept**	-	MD **11.9 lower** (5.58 lower to 18.22 lower)
Parent global assessment of child's overall well being (VAS)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **6.1 lower** (13.12 lower to 0.92 higher)
CHAQ disability index											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **0.1 lower** (0.37 lower to 0.17 higher)
ESR (mm/hr)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **4.7 lower** (13.94 lower to 4.54 higher)
CRP (mg/dL)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	62	60	-		MD **0.12 lower** (0.25 lower to 0.01 higher)
Improvement, achievement of ACR 30											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	43/62 (69.4%)	49/60 (81.7%)	**RR 1.18** (0.96 to 1.44)	694 per 1,000	**125 more per 1,000** (28 fewer to 305 more)
ACR 50											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	32/62 (51.6%)	46/60 (76.7%)	**RR 1.49** (1.12 to 1.96) **Favors abatacept**	516 per 1,000	**253 more per 1,000** (62 more to 495 more)
ACR 70											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	19/62 (30.6%)	32/60 (53.3%)	**RR 1.74** (1.12 to 2.71) **Favors abatacept**	306 per 1,000	**227 more per 1,000** (37 more to 524 more)
ACR 90											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	10/62 (16.1%)	24/60 (40.0%)	**RR 2.48** (1.30 to 4.73) **Favors abatacept**	161 per 1,000	**239 more per 1,000** (48 more to 602 more)
Inactive disease											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	7/62 (11.3%)	18/60 (30.0%)	**RR 2.66** (1.20 to 5.90) **Favors abatacept**	113 per 1,000	**187 more per 1,000** (23 more to 553 more)
Total serious adverse events											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
252 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	2/62 (3.2%)	6/190 (3.2%)	**RR 0.98** (0.20 to 4.73)	32 per 1,000	**1 fewer per 1,000** (26 fewer to 120 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. not applicable

b. All patients had received prior DMARDs and most patients in both arms received concurrent MTX

c. Confidence interval wide and includes line of no difference

d. Confidence interval crosses the line of no difference

Table 2. Long-term Open Label Extension Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ruperto 2010[3]	Long term open label extension of RCT	All patients had received treatment for at least 21 months	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (data from 120 patients) ACR 30: 103/120 (85.83%) ACR 50: 98/120 (81.67%) ACR 70: 83/120 (69.17%) ACR 90: 52/120 (43.33%) ACR 100: 30/120 (25%) SAE: 23/153 (15.03%) patients reported a SAE
Lovell 2015[4]	Long term open label	Patients had received	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (Intention-to-treat data from 190 patients, assuming dropouts and patients with missing data were non-

	extension of RCT	treatment for up to 7 years			responders) ACR 30: 35.3% (95% CI 28.5–42.1%) ACR 50: 33.7% (95% CI 27.0–40.4%) ACR 70: 27.4% (95% CI 21.0–33.7%) ACR 90: 20.5% (95% CI 14.8–26.3%) ACR 100: 16.3% (95% CI 11.1–21.6%) SAE: 30/153 (19.6%) patients reported a SAE

References

1. Ruperto N, Lovell DJ, Li T, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M, et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2010;62(11):1542-1551.

2. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383-391.

3. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(6):1792-1802.

4. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety, efficacy and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arth Rheum 2015; 67(10):2759-2770.

PICO 16. In children and adolescents with JIA and polyarthritis, should tocilizumab monotherapy versus tocilizumab + non-biologic DMARD be recommended?

Summary: This PICO was addressed by one RCT in a direct drug comparison.[1] Results show no statistically significant differences in JIA ACR 70, JIA ACR 90, and serious adverse events. Of the 188 patients enrolled in the open-label tocilizumab part of the study, one patient had a positive anti-tocilizumab antibody assay and withdrew from the study due to lack of efficacy.

Overall quality of evidence across all critical outcomes: Low

Tocilizumab (8mg/kg or 10mg/kg) + Methotrexate compared to Tocilizumab at 40 weeks for health problem or population [1]

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Tocilizumab at 40 weeks	With Tocilizumab (8mg/kg or 10mg/kg) + MTX		Risk with Tocilizumab at 40 weeks	Risk difference with Tocilizumab (8mg/kg or 10mg/kg) + MTX
JIA ACR70											
82 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	8/15 (53.3%)	45/67 (67.2%)	**RR 1.26** (0.76 to 2.08)	533 per 1,000	**139 more per 1,000** (128 fewer to 576 more)
JIA ACR90											
82 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	5/15 (33.3%)	32/67 (47.8%)	**RR 1.43** (0.67 to 3.06)	333 per 1,000	**143 more per 1,000** (110 fewer to 687 more)
Serious Adverse Events											

Tocilizumab (8mg/kg or 10mg/kg) + Methotrexate compared to Tocilizumab at 40 weeks for health problem or population [1]

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
163 (1 RCT)	not serious	not serious	serious [c]	serious [b]	none	⨁⨁◯◯ LOW	3/81 (3.7%)	3/82 (3.7%)	**RR 0.99** (0.21 to 4.75)	37 per 1,000	**0 fewer per 1,000** (29 fewer to 139 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Randomization, allocation, and blinding not mentioned

b. C.I. crosses no effect line

c. Tocilizumab vs. placebo patients

References

1. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

PICO 17: In children and adolescents with JIA and polyarthritis on NSAID therapy and no risk factors, should continued NSAID monotherapy versus addition of non-biologic DMARD as initial therapy be recommended?

Summary: This PICO was addressed by direct comparison in three placebo-controlled RCTs,[1-3] indirectly by one prospective observational study,[4] and by one retrospective observational study evaluating methotrexate.[5] All patients in the placebo-controlled trials were receiving NSAIDS.

Low-dose methotrexate was favored over placebo for one efficacy outcome (change in number of joints with limitation of motion) in one small RCT (n=77, Table 1).[1] Sulfasalazine was favored over placebo for the majority of efficacy outcomes (including ACR 30 and remission) in two RCTs enrolling 61 to 69 patients (Table 3).[2,3] The primary van Rossum trial was a 24-week trial conducted in 1998, while the 2007 van Rossum trial measured outcomes at a median of 9 years. Only 3 SAEs were reported in SSZ patients in the earlier trial.[2]

One observational study reported no significant differences for total SAEs in 372 polyarthritis patients on NSAIDS vs. off NSAIDS[4](Table 2). Lastly, one retrospective observational study evaluating methotrexate in 123 polyarthritis patients indicated that longer duration of methotrexate (>4/≤ 4 years) was significantly associated with no inactive disease (OR 2.67; 95% CI: 1.08 to 6.62; p<0.05)(Table 4).[5]

Overall quality of evidence across all critical outcomes: Moderate

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Giannini EH, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Low-Dose MTX		Risk with Placebo	Risk difference with Low-Dose MTX
Change in Articular Severity Score, 6 mos (composite of joint swelling, pain, tenderness, limitation of range of motion)											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Giannini EH, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

Quality assessment							Summary of findings				
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38		-	MD **26.6 lower** (138.85 lower to 85.65 higher)
Change in number of joints with pain on ROM, 6 mos											
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38	-	-	MD **3.9 lower** (9.86 lower to 2.06 higher)
Change in number of joints with tenderness, 6 mos											
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38	-	-	MD **3.8 lower** (9.62 lower to 2.02 higher)
Change in duration of morning stiffness, 6 mos											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Giannini EH, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

Quality assessment							Summary of findings				
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38	-	-	MD **10.5 lower** (48.06 lower to 27.06 higher)
Change in number of joints with active arthritis, 6 mos											
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38	-	-	MD **2.3 lower** (8.18 lower to 3.58 higher)
Change in number of joints with limitation of motion, 6mos											
77 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	39	38	**Favors low-dose MTX**	-	MD **4.7 lower** (8.89 lower to 0.51 lower)
Change in number of joints with swelling, 6 mos											

Table 1. Low-Dose Methotrexate compared to Placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Giannini EH, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.

Quality assessment							Summary of findings				
77 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	39	38	-	-	MD **2.8 lower** (7.27 lower to 1.67 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Not applicable

b. Small single study. 95% CI includes the line of no difference.

c. Small single study

Table 2. NSAID compared to Off NSAID for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Sobel RE, Lovell DJ, Brunner HI, Weiss JE, Morris PW, Gottlieb BS, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the Phase 4 registry. Pediatr Rheumatol Online J. 2014;12:29.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Off NSAID	**With NSAID**		**Risk with Off NSAID**	**Risk difference with NSAID**

Table 2. NSAID compared to Off NSAID for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: Sobel RE, Lovell DJ, Brunner HI, Weiss JE, Morris PW, Gottlieb BS, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the Phase 4 registry. Pediatr Rheumatol Online J. 2014;12:29.

Quality assessment							Summary of findings				
Total serious adverse events											
372 (1 observational study)	very serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	4/79 (5.1%)	14/293 (4.8%)	**RR 0.94** (0.32 to 2.79)	51 per 1,000	**3 fewer per 1,000** (34 fewer to 91 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Prospective, non-randomized, no blinding

b. Not applicable

c. Indirect comparison

d. Single study, 95% CI includes the line of no difference.

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings		
№ of participants	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of**	**Study event rates (%)**	**Relative effect**	**Anticipated absolute effects**

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
(studies) Follow-up	bias					evidence	With placebo	With SSZ	(95% CI)	Risk with placebo	Risk difference with SSZ
ACR30, median 9yrs											
61 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	5/29 (17.2%)	15/32 (46.9%)	**OR 4.24** (1.29 to 13.89) **Favors SSZ**	172 per 1,000	**297 more per 1,000** (39 more to 571 more)
Remission, median 9yrs											
61 (1 RCT)	not serious	not serious [a]	not serious	serious [e]	none	⊕⊕⊕◯ MODERATE	1/29 (3.4%)	8/32 (25.0%)	**OR 9.33** (1.09 to 80.06) **Favors SSZ**	34 per 1,000	**215 more per 1,000** (3 more to 706 more)
Remission between primary study and f/u, median 9yrs											
61 (1 RCT)	not serious	not serious [a]	not serious	serious [f]	none	⊕⊕⊕◯ MODERATE	4/29 (13.8%)	13/32 (40.6%)	**OR 4.28** (1.20 to 15.22) **Favors SSZ**	138 per 1,000	**269 more per 1,000** (23 more to 571 more)
At least 50% improvement, 24w											

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
69 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	15/34 (44.1%)	23/35 (65.7%)	**OR 2.43** (0.92 to 6.42)	441 per 1,000	**216 more per 1,000** (20 fewer to 394 more)
At least 30% improvement, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	7/34 (20.6%)	15/35 (42.9%)	**OR 2.89** (0.99 to 8.41)	206 per 1,000	**222 more per 1,000** (2 fewer to 480 more)
Number of joints with limitation of motion, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	34	35	-	-	MD **0.52 lower** (3.22 lower to 2.18 higher)
Number of active joints, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **4.76 lower** (8.06 lower to 1.46 lower)

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
Patients' score of disease activity, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **0.68 lower** (1.18 lower to 0.18 lower)
Parents' score of disease activity, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **0.54 lower** (0.96 lower to 0.12 lower)
Physicians' score of disease activity, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **0.96 lower** (1.47 lower to 0.45 lower)
ESR, 24w											

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **0.7 lower** (0.91 lower to 0.49 lower)
CRP, 24w											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	34	35	**Favors SSZ**	-	MD **0.44 lower** (0.83 lower to 0.05 lower)
Toxic reaction with anorexia											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [d]	none	⊕⊕⊕◯ MODERATE	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**
Cervical lymphadenopathy											
69 (1 RCT)	not serious	not serious [a]	not serious	serious [d]	none	⊕⊕⊕◯ MODERATE	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**
Increased liver transaminase levels (3x over baseline)											

Table 3. Sulfasalazine compared to placebo for patients with polyarthritis on NSAID therapy and no risk factors

Bibliography: van Rossum MA, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
van Rossum MA, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

Quality assessment							Summary of findings				
69 (1 RCT)	not serious	not serious [a]	not serious	serious [d]	none	⊕⊕⊕◯ MODERATE	0/34 (0.0%)	1/35 (2.9%)	**OR 3.00** (0.12 to 76.24)	0 per 1,000	**Not calculable**

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Not applicable

b. Small single study. 95% CI includes the line of no difference.

c. Small single study

d. Small single study with only 1 event

e. Small single study. Very wide CI.

f. Small single study. Wide CI.

Table 4. Studies with Additional Relevant Data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
410, van Rossum, 2007	RCT	Median 9 years	61 patients with polyarticular JIA	SSZ: n=32 Placebo: n=29	Median (IQR) scores for active joints were lower for SSZ vs placebo (2 [0 to 3] SSZ, 4 [1 to 7] placebo; p<0.05)
					Median (IQR) scores for limited joints were lower for SSZ vs placebo (4 [1 to 12] SSZ, 7 [3 to 13] placebo; p value not reported)
					Median (IQR) scores for Physician Global Assessment of Disease Activity were lower for SSZ vs placebo (1.5 [0 to 2] SSZ, 2 [1 to 3]

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					placebo; p value not reported)
					Median (IQR) scores for ESR were lower for SSZ vs placebo (6 [4 to 18] SSZ, 10 [7 to 26] placebo; p value not reported).
					Median (IQR) scores for CHAQ were similar (0.25 [0 to 1.8) SSZ, 0.25 [0 to 2] placebo; p value not reported)
					Significantly more SSZ patients achieved ACR30 vs placebo (47% SSZ vs. 17% placebo; p<0.05)
					Significantly more SSZ patients achieved remission vs placebo (25% SSZ vs. 3% placebo; p<0.05).
					Significantly more SSZ patients had episodes of remission between primary SSZ trial and followup trial vs placebo (41% SSZ vs. 14% placebo; p<0.05)
363, Magnani, 2009 [5]	Retrospective cohort	Nov 1986-Feb 2002	123 patients with polyarticular JIA	Methotrexate (dose and duration of treatment not defined) Disease inactivity defined as (active joint count = 0, physicians global, absence of systemic symptoms, no uveitis, negative acute phase reactants.	Longer duration of MTX (>4/≤ 4 years) significantly associated with no inactive disease (OR 2.67, 95% CI: 1.08 to 6.62; p<0.05)

References:

1. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med. 1992;326(16):1043-1049.
2. van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum. 1998;41(5):808-816.
3. van Rossum MA, van Soesbergen RM, Boers M, Zwinderman AH, Fiselier TJ, Franssen MJ, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis. 2007;66(11):1518-1524.

4. Sobel RE, Lovell DJ, Brunner HI, Weiss JE, Morris PW, Gottlieb BS, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the Phase 4 registry. Pediatr Rheumatol Online J. 2014;12:29.
5. Magnani A, Pistorio A, Magni-Manzoni S, Falcone A, Lombardini G, Bandeira M, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. J Rheumatol. 2009;36(3):628-634.

PICO 18. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with triple non-biologic DMARD versus methotrexate monotherapy as initial therapy be recommended?

Summary: This PICO question was addressed by one open-label clinical trial.[1] Patients in this trial participated in one of three arms: infliximab + MTX, MTX alone, and MTX+ sulfasalazine + hydroxychloroquine (COMBO). No significant differences were reported for all outcomes including ACR Pedi 75, inactive disease, drug survival, mean state of inactive disease, and CHAQ change at 54 weeks. Three MTX patients were hospitalized for infections.

Overall quality of evidence for all critical outcomes: Low

MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Triple DMARD	With MTX		Risk with Triple DMARD	Risk difference with MTX
ACR Pedi 75											
40 (1 RCT)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁⨁◯◯ LOW	13/20 (65.0%)	10/20 (50.0%)	**OR 0.54** (0.15 to 1.92)	650 per 1,000	**149 fewer per 1,000** (432 fewer to 131 more)
Inactive Disease											

MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
40 (1 RCT)	serious [a]	not serious [b]	not serious	serious [c]	none	⊕⊕◯◯ LOW	8/20 (40.0%)	5/20 (25.0%)	**OR 0.50** (0.13 to 1.93)	400 per 1,000	**150 fewer per 1,000** (320 fewer to 163 more)
Mean State of Inactive Disease (weeks)											
40 (1 RCT)	serious [a]	not serious [b]	not serious	serious [d]	none	⊕⊕◯◯ LOW	20	20	-	-	MD **7 lower** (14.67 lower to 0.67 higher)
CHAQ change at 54 weeks											
40 (1 RCT)	serious [a]	not serious [b]	not serious	serious [c]	none	⊕⊕◯◯ LOW	20	20	-	-	MD **0.27 lower** (0.55 lower to 0.01 higher)
Serious Adverse Events											
40 (1 RCT)	serious [a]	not serious [b]	not serious	serious [e]	none	⊕⊕◯◯ LOW	0/20 (0.0%)	3/20 (15.0%)	**RR 7.00** (0.38 to 127.32)	0 per 1,000	**Not estimable**

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Open label study

b. Not applicable

c. Small study. 95% CI overlaps the line of no difference.

d. Small study. Wide CI overlaps the line of no difference.

e. Small study with very few events.

References

1. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011;70(9):1605-1612.

PICO 19: **In children and adolescents with JIA and polyarthritis**, no risk factors, should initial therapy with triple non-biologic DMARD or TNFi as initial therapy be recommended?

Summary: This PICO question was addressed by one open-label clinical trial.[1] Patients in this trial participated in one of three arms: infliximab + MTX, MTX alone, and MTX+ sulfasalazine + hydroxychloroquine (COMBO). This study is indirect in that it does not use a TNFi in isolation; infliximab was always used with the DMARD MTX in this study. Furthermore, only the TNFi infliximab was used to address the question. The data regarding methotrexate alone was excluded from this analysis, as this was not a part of the PICO question. This study directly addressed polyarticular JIA patients, however, it was open label and there was no blinding of participants. The authors found a significantly higher proportion of patients in the TNFi arm achieved an ACR Pedi 75 compared to the COMBO arm (p=0.0005), however the findings were imprecise due to the small number of patients. There was also a significantly higher percentage of patients with inactive disease in the TNF group compared to COMBO (p=0.05). The TNFi group also had a significant higher number of weeks of inactive disease compared to the COMBO counterparts (p=0.044). There were no serious adverse events of interest (in this situation defined as infection requiring hospitalization, hospitalization, malignancy). There was evidence of infection however, with 36 infections identified in the TNF group and 35 in the COMBO group.

Overall quality of evidence for all critical outcomes: Low

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Triple DMARD	With TNFi and MTX		Risk with Triple DMARD	Risk difference with TNFi and MTX
ACR Pedi 75											

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
39 (1 RCT)	serious [a]	not serious [b]	not serious	serious [c]	none	□□◯◯ LOW	13/20 (65.0%)	19/19 (100.0%)	**OR 21.67** (1.14 to 412.15) **Favors TNFi + MTX**	650 per 1,000	**326 more per 1,000** (29 more to 349 more)
Inactive Disease											
39 (1 RCT)	serious [a]	not serious [b]	not serious	serious [d]	none	□□◯◯ LOW	8/20 (40.0%)	13/19 (68.4%)	**OR 3.25** (0.87 to 12.14)	400 per 1,000	**284 more per 1,000** (33 fewer to 490 more)
Mean State of Inactive Disease (weeks)											
39 (1 RCT)	serious [a]	not serious [b]	not serious	not serious	none	□□□◯ MODERATE	20	19	**Favors TNFi + MTX**	-	MD **13 higher** 2.92 higher to 23.08 higher)
CHAQ change at 54 weeks											

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
39 (1 RCT)	serious [a]	not serious [b]	not serious	serious [d]	none	□□◯◯ LOW	20	19	-	-	MD **0.1 lower** (0.38 lower to 0.18 higher)
Serious Adverse Events											
40 (1 RCT)	not serious	not serious [b]	not serious	very serious [e]	none	□□◯◯ LOW	0/20 (0.0%)	0/20 (0.0%)	not estimable	0 per 1,000	not estimable

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. open label study

b. not applicable

c. small study with wide confidence interval

d. confidence interval overlaps the line of no difference

e. sample size too small to rule out serious adverse events

References

1. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011;70(9):1605-1612.

PICO 20: In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus TNFi as initial therapy be recommended?

SUMMARY: This PICO was addressed by one placebo-controlled RCT (both indirect and direct drug comparisons)[1] and two observational study direct drug comparisons.[2,3] Both observational studies had an indirect study population (most patients had received prior DMARDs), and 21% of patients receiving adalimumab in the RCT had received prior methotrexate. Results for the direct drug comparisons between adalimumab vs. methotrexate and etanercept vs. methotrexate show no statistically significant differences in ACR 30/50/70/90 (Table 1),[1] Physician's Global Assessment Score of 0, and Total Active Joint Count at 36 months (Table 3).[3] There were mixed findings for SAE for adalimumab vs. methotrexate; the RCT[1] showed no significant difference (but there were two few events to rule out a difference), and the observational study showed significantly fewer events in the methotrexate group (Table 1). The methotrexate group also had significantly fewer events than the etanercept group (Table 3)[2] and in the other observational study methotrexate had lower exposure-adjusted rates of SAE per 100 patient-years (4.6 vs. 7.1, Table 4).[3] There was no significant difference between etanercept vs. methotrexate for total medically important infections (Table 3).[3] Results for the indirect drug comparison (adalimumab vs. placebo) showed no significant difference for ACR 30/50/70/90 with no SAEs reported (Table 2).

Overall quality of evidence across all critical outcomes: Low

Table 1. ADA monotherapy compared to MTX in polyarticular JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820. Klotsche J, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With MTX, RCT, 48wks	With ADA monotherapy		Risk with MTX, RCT, 48wks	Risk difference with ADA monotherapy
ACR 30											

Table 1. ADA monotherapy compared to MTX in polyarticular JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820. Klotsche J, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.

Quality assessment							Summary of findings				
67 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	None	⊕⊕◯◯ LOW	14/37 (37.8%)	17/30 (56.7%)	**RR 1.50** (0.89 to 2.51)	378 per 1,000	**189 more per 1,000** (42 fewer to 571 more)
ACR 50											
67 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	None	⊕⊕◯◯ LOW	14/37 (37.8%)	16/30 (53.3%)	**RR 1.41** (0.83 to 2.40)	378 per 1,000	**155 more per 1,000** (64 fewer to 530 more)
ACR 70											
67 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	None	⊕⊕◯◯ LOW	10/37 (27.0%)	14/30 (46.7%)	**RR 1.73** (0.90 to 3.32)	270 per 1,000	**197 more per 1,000** (27 fewer to 627 more)
ACR 90											
67 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	None	⊕⊕◯◯ LOW	10/37 (27.0%)	9/30 (30.0%)	**RR 1.11** (0.52 to 2.38)	270 per 1,000	**30 more per 1,000** (130 fewer to 373 more)
SAE (RCT)											

Table 1. ADA monotherapy compared to MTX in polyarticular JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820. Klotsche J, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.

Quality assessment							Summary of findings				
67 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	None	⨁⨁◯◯ LOW	1/37 (2.7%)	0/30 (0.0%)	**RR 0.41** (0.02 to 9.68)	27 per 1,000	**16 fewer per 1,000** (26 fewer to 235 more)
SAE (Observational study)											
1101 (1 observational study)	serious [e]	not serious [a]	serious [f]	not serious	none	⨁⨁◯◯ LOW	75/1055 (7.1%)	23/46 (50.0%)	**RR 7.03** (4.90 to 10.10) **Favors MTX**	71 per 1,000	**429 more per 1,000** (277 more to 647 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Not applicable

b. 21% of patients in the Ada group had received prior methotrexate.

c. Small single study. 95% CI includes the line of no difference.

d. Small single study with only 1 event. Very wide 95% CI that overlaps the line of no difference.

e. Prospective, non-randomized, no blinding

f. Indirect population

Table 2. ADA compared to Placebo in polyarticular JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo, RCT, 48wks	**With ADA**		**Risk with Placebo, RCT, 48wks**	**Risk difference with ADA**
ACR 30											
58 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/28 (32.1%)	17/30 (56.7%)	**OR 2.76** (0.94 to 8.07)	321 per 1,000	**245 more per 1,000** (13 fewer to 471 more)
ACR 50											
58 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/28 (32.1%)	16/30 (53.3%)	**OR 2.41** (0.83 to 7.03)	321 per 1,000	**212 more per 1,000** (39 fewer to 448 more)
ACR 70											
58 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	8/28 (28.6%)	14/30 (46.7%)	**OR 2.19** (0.74 to 6.50)	286 per 1,000	**181 more per 1,000** (57 fewer to 437 more)
ACR 90											
58 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	5/28 (17.9%)	9/30 (30.0%)	**OR 1.97** (0.57 to 6.83)	179 per 1,000	**121 more per 1,000** (68 fewer to 419 more)

Table 2. ADA compared to Placebo in polyarticular JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Quality assessment							Summary of findings				
SAE											
58 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/28 (0.0%)	0/30 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison

c. Small single study. Wide 95% CI that overlaps the line of no difference.

d. Small single study with no events

Table 3. ETN compared to MTX in polyarticular JIA

Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With MTX, cohort B	**With ETN**		**Risk with MTX, cohort B**	**Risk difference with ETN**
Total medically important infections											

Table 3. ETN compared to MTX in polyarticular JIA

Giannini EH, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804.

Quality assessment							Summary of findings				
300 (1 observational study)	very serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	4/103 (3.9%)	5/197 (2.5%)	**OR 0.64** (0.17 to 2.45)	39 per 1,000	**14 fewer per 1,000** (32 fewer to 51 more)
Physician's global assessment score of 0, 36mos											
109 (1 observational study)	very serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	17/42 (40.5%)	31/67 (46.3%)	**OR 1.27** (0.58 to 2.77)	405 per 1,000	**59 more per 1,000** (122 fewer to 248 more)
Total active joint score of 0, 36mos											
108 (1 observational study)	very serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	24/42 (57.1%)	43/66 (65.2%)	**OR 1.40** (0.63 to 3.10)	571 per 1,000	**80 more per 1,000** (115 fewer to 234 more)
SAE											
2217 (1 observational study)	serious [e]	not serious [b]	serious [f]	serious [c]	none	⊕◯◯◯ VERY LOW	75/1055 (7.1%)	199/1162 (17.1%)	**RR 2.41** (1.87 to 3.10) **Favors MTX**	71 per 1,000	**100 more per 1,000** (62 more to 149 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Retrospective, non-randomized, no blinding

b. Not applicable

c. Indirect population (most patients had received prior DMARDs)

d. Single study. 95% CI includes the line of no difference.

e. Prospective, non-randomized, no blinding

f. Indirect population

Table 4. Additional Data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
341, Giannini, 2009	Cohort study	3 years	300 patients with polyarticular JIA	Etanercept: 103 MTX: 197	Exposure-adjusted rates of serious adverse events per 100 patient-years were higher with Etanercept (7.1 Etanercept, 4.6 MTX).

References

1. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.
2. Klotsche J, Niewerth M, Haas JP, Huppertz HI, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.
3. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804.

PICO 21. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus abatacept as initial therapy be recommended?

Summary: Literature searches revealed three studies (2 RCTs and 1 open label extension) which seemed to indirectly address the PICO question (all patients had received prior DMARDs and most patients in both arms received concurrent methotrexate). Of the two RCTs, however, the data from one study[1] was not abstracted as both studies[1,2] included the same study population (both part of the AWAKEN trial). Ruperto 2008[2] included data from patients who dropped out in addition to those who remained in the study, while the other study[1] only analyzed those patients who remained in the study and thus was not a good representation of treatment efficacy. Ruperto[2] demonstrated that patients on abatacept significantly improved in terms of their number of active joints, number of joints with limited ROM, physician's global assessment, and CHAQ disability index compared to placebo (Table 1). The measurement for the disability index was imprecise, however, the remaining measurements remained significant. There was also a significantly higher number of patients in the abatacept group vs. placebo group who achieved an ACR Pedi 50/70/90 compared to controls. The difference in ACR Pedi 30 was not significant. There was no statistically significant difference in terms of serious adverse events between the groups. This study was an indirect representation of the PICO question as it compared abatacept to placebo (74% of patients were also receiving methotrexate in both groups) but not abatacept to a second DMARD. In addition, the study population included more than just polyarticular JIA patients. There was also no delineation between patients with risk factors and without which makes this indirect as the PICO question asked specifically about poly-JIA patients without risk factors.

An open-label extension study[3, 4] investigated improvement in patients from the initial AWAKEN trial over time (Table 2). As such, the same limitations about the indirectness of the population studied apply here. Researchers found that 19.6% of patients reported experiencing a serious adverse event by the end of the long-term extension period (up to 7 years). The majority of patients (85%) achieved an ACR 30, and 43% were found to achieve an ACR 90. However, these numbers dropped to 35% and 20.5% in an intention-to-treat analysis that assumed any dropouts or patients with missing data were non-responders. Authors concluded that patients on abatacept overall achieved clinically meaningful responses over the long-term.

Quality of evidence across all critical outcomes: Low

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
(studies) Follow-up	bias					evidence	With Placebo end of 6 month period	With Abatacept	(95% CI)	Risk with Placebo end of 6 month period	Risk difference with Abatacept
Number of joints with active arthritis											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⊕⊕⊕◯ MODERATE	62	60	**Favors abatacept**	-	MD **3.1 lower** (0.93 lower to 5.27 lower)
Physician Global Assessment of child's well being (VAS)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⊕⊕⊕◯ MODERATE	62	60	**Favors abatacept**	-	MD **11.9 lower** (5.58 lower to 18.22 lower)
Parent global assessment of child's overall well being (VAS)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **6.1 lower** (13.12 lower to 0.92 higher)
CHAQ disability index											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **0.1 lower** (0.37 lower to 0.17 higher)
ESR (mm/hr)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **4.7 lower** (13.94 lower to 4.54 higher)
CRP (mg/dL)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	62	60	-		MD **0.12 lower** (0.25 lower to 0.01 higher)
Improvement, achievement of ACR 30											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	43/62 (69.4%)	49/60 (81.7%)	**RR 1.18** (0.96 to 1.44)	694 per 1,000	**125 more per 1,000** (28 fewer to 305 more)
ACR 50											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	32/62 (51.6%)	46/60 (76.7%)	**RR 1.49** (1.12 to 1.96) **Favors abatacept**	516 per 1,000	**253 more per 1,000** (62 more to 495 more)
ACR 70											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	19/62 (30.6%)	32/60 (53.3%)	**RR 1.74** (1.12 to 2.71) **Favors abatacept**	306 per 1,000	**227 more per 1,000** (37 more to 524 more)
ACR 90											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	10/62 (16.1%)	24/60 (40.0%)	**RR 2.48** (1.30 to 4.73) **Favors abatacept**	161 per 1,000	**239 more per 1,000** (48 more to 602 more)
Inactive disease											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	7/62 (11.3%)	18/60 (30.0%)	**RR 2.66** (1.20 to 5.90) **Favors abatacept**	113 per 1,000	**187 more per 1,000** (23 more to 553 more)
Total serious adverse events											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
252 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	2/62 (3.2%)	6/190 (3.2%)	**RR 0.98** (0.20 to 4.73)	32 per 1,000	**1 fewer per 1,000** (26 fewer to 120 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. not applicable

b. All patients had received prior DMARDs and most patients in both arms received concurrent MTX

c. Confidence interval wide and includes line of no difference

d. Confidence interval crosses the line of no difference

Table 2. Long-term Open Label Extension Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ruperto 2010[3]	Long term open label extension of RCT	All patients had received treatment for at least 21 months	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (data from 120 patients) ACR 30: 103/120 (85.83%) ACR 50: 98/120 (81.67%) ACR 70: 83/120 (69.17%) ACR 90: 52/120 (43.33%) ACR 100: 30/120 (25%) SAE: 23/153 (15.03%) patients reported a SAE
Lovell 2015[4]	Long term open label	Patients had received	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (Intention-to-treat data from 190 patients, assuming dropouts and patients with missing data were non-

	extension of RCT	treatment for up to 7 years			responders) ACR 30: 35.3% (95% CI 28.5–42.1%) ACR 50: 33.7% (95% CI 27.0–40.4%) ACR 70: 27.4% (95% CI 21.0–33.7%) ACR 90: 20.5% (95% CI 14.8–26.3%) ACR 100: 16.3% (95% CI 11.1–21.6%) SAE: 30/153 (19.6%) patients reported a SAE

References

1. Ruperto N, Lovell DJ, Li T, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M, et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2010;62(11):1542-1551.

2. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383-391.

3. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(6):1792-1802.

4. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety, efficacy and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arth Rheum 2015; 67(10):2759-2770.

PICO 22. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus tocilizumab as initial therapy be recommended?

Summary: This PICO was addressed by one RCT in a direct drug comparison.[1] However, the population was indirect because the majority of paitents (71%) had received prior DMARDs. Results show no statistically significant differences in JIA ACR 70 or JIA ACR 90, but the findings were imprecise due to wide 95% CIs that crossed the line of no difference.

Overall quality of evidence across all critical outcomes: Very low

Tocilizumab (8mg/kg or 10mg/kg) compared to Methotrexate for health problem or population

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Methotrexate	With Tocilizumab (8mg/kg or 10mg/kg)		Risk with Methotrexate	Risk difference with Tocilizumab (8mg/kg or 10mg/kg)
JIA ACR 70											
79 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	30/64 (46.9%)	8/15 (53.3%)	**RR 1.14** (0.66 to 1.95)	469 per 1,000	**66 more per 1,000** (159 fewer to 445 more)
JIA ACR 90											
79 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	18/64 (28.1%)	5/15 (33.3%)	**RR 1.19** (0.52 to 2.68)	281 per 1,000	**53 more per 1,000** (135 fewer to 473 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Randomization, allocation, and blinding not mentioned

b. Indirect population (most patients received prior DMARDs)

c. Wide 95% C.I. crosses no effect line

References

1. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

PICO 23. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with TNFi versus tocilizumab as initial therapy be recommended?

Summary: This PICO was addressed by one observational study[1] in a direct drug comparison between tocilizumab vs. adalimumab (Table 1) and tocilizumab vs. etanercept (Table 2). However, the study population was somewhat indirect in that a large proportion of patients were receiving concurrent methotrexate treatment. Results show no statistically significant differences in JIA ACR 30, 50, 70, or 90, although for all but ACR the findings were imprecise due to wide 95% CIs. There were no statistically significant differences in JADAS10 or a reduction in CHAQ-DI. In regard to SAEs, tocilizumab had statistically significantly fewer events than etanercept. Tocilizumab also had fewer SAEs than adalimumab but the difference was imprecise and not statistically significant.

Overall quality of evidence across all critical outcomes: Very low

Table 1. Tocilizumab compared to ADA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With ADA	With Tocilizumab		Risk with ADA	Risk difference with Tocilizumab
JADAS10											
310 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	236	74	-	-	MD **2.2 lower** (6.04 lower to 1.64 higher)
ACR 30 at 3 months											

Table 1. Tocilizumab compared to ADA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
310 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	158/236 (66.9%)	45/74 (60.8%)	**RR 0.91** (0.74 to 1.11) **No difference**	669 per 1,000	**60 fewer per 1,000** (174 fewer to 74 more)
ACR 50 at 3 months											
310 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	139/236 (58.9%)	38/74 (51.4%)	**RR 0.87** (0.68 to 1.12)	589 per 1,000	**77 fewer per 1,000** (188 fewer to 71 more)
ACR 70 at 3 months											
310 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	101/236 (42.8%)	26/74 (35.1%)	**RR 0.82** (0.58 to 1.16)	428 per 1,000	**77 fewer per 1,000** (180 fewer to 68 more)
ACR 90 at 3 months											
310 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	64/236 (27.1%)	19/74 (25.7%)	**RR 0.95** (0.61 to 1.47)	271 per 1,000	**14 fewer per 1,000** (106 fewer to 127 more)
Reduction in CHAQ-DI											

Table 1. Tocilizumab compared to ADA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
310 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	236	74	-	The mean reduction in CHAQ-DI was **0**	MD **0.19 higher** (0.07 higher to 0.31 higher)
SAE											
310 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	26/236 (11.0%)	3/74 (4.1%)	**RR 0.37** (0.11 to 1.18)	110 per 1,000	**69 fewer per 1,000** (98 fewer to 20 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. No randomization, allocation concealment, or blinding

b. Indirect population (large proportion of patients had concurrent methotrexate)

c. Wide 95% C.I. crosses no effect line

Table 2. Tocilizumab compared to ETA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ETA	**With Tocilizumab**		**Risk with ETA**	**Risk difference with Tocilizumab**

Table 2. Tocilizumab compared to ETA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
JADAS10											
493 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	419	74	-	-	MD **3.5 lower** (7.15 lower to 0.15 higher)
ACR 30 at 3 months											
493 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	285/419 (68.0%)	45/74 (60.8%)	**RR 0.89** (0.74 to 1.09) **No difference**	680 per 1,000	**75 fewer per 1,000** (177 fewer to 61 more)
ACR 50 at 3 months											
493 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	251/419 (59.9%)	38/74 (51.4%)	**RR 0.86** (0.68 to 1.08)	599 per 1,000	**84 fewer per 1,000** (192 fewer to 48 more)
ACR 70 at 3 months											
493 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	176/419 (42.0%)	26/74 (35.1%)	**RR 0.84** (0.60 to 1.16)	420 per 1,000	**67 fewer per 1,000** (168 fewer to 67 more)
ACR 90 at 3 months											

Table 2. Tocilizumab compared to ETA for patients with JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
493 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	101/419 (24.1%)	19/74 (25.7%)	**RR 1.07** (0.70 to 1.63)	241 per 1,000	**17 more per 1,000** (72 fewer to 152 more)
Reduction in CHAQ-DI											
493 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	419	74	-	-	MD **0.09 higher** (0.03 lower to 0.21 higher)
SAE											
493 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	119/419 (28.4%)	3/74 (4.1%)	**RR 0.14** (0.05 to 0.44) **Favors tocilizumab**	284 per 1,000	**244 fewer per 1,000** (270 fewer to 159 fewer)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. No randomization, allocation concealment, or blinding. Retrospective study with high risk of selection bias.

b. Indirect population (large proportion of patients had concurrent methotrexate)

c. Wide 95% C.I. crosses no effect line

References

1. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

PICO 24. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with TNFi versus abatacept as initial therapy be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. However, a recent systematic review performed a network meta-analysis of placebo-controlled trials of TNFis and abatacept to indirectly compare treatment efficacy of these medications in patients with JIA. Adalimumab and abatacept showed no significant difference for the outcomes ACR 50 (RR 1.12, 95% CI 0.65 to 1.96) and ACR 70 (RR 1.34, 95% CI 0.65 to 2.79), but the 95% CIs are imprecise. Etanercept and abatacept also showed no significant difference for ACR 50 (RR 2.1, 95% CI 0.95 to 4.64) and ACR 70 (RR 1.31, 95% CI 0.48 to 3.60), but again there was imprecision in the CIs. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. Due to the indirectness of the comparison and imprecision in effect estimates, the overall quality of evidence is low.

Quality of evidence across all critical outcomes: Low

References

1. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess 2016;20(34).

PICO 25. In children and adolescents with JIA and polyarthritis and no risk factors, should initial therapy with abatacept versus tocilizimab as initial therapy be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. However, a recent systematic review performed a network meta-analysis of placebo-controlled trials of tocilizumab and abatacept to indirectly compare treatment efficacy of these medications in patients with JIA. Abatacept and tocilizumab did not show significant differences in ACR 50 (RR 1.05, 95% CI 0.72 to 1.53) or ACR 70 (RR 1.13, 95% CI 0.66 to 1.93), but the effect estimates were imprecise due to wide 95% CIs. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. Due to the indirectness of the comparison and imprecision in effect estimates, the overall quality of evidence is low.

Quality of evidence across all critical outcomes: Low

References

1. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess 2016;20(34).

PICO 26. In children and adolescents with JIA and polyarthritis plus risk factors receiving NSAIDs, should continued NSAID monotherapy versus the addition of non-biologic DMARD as initial therapy be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 27. In children and adolescents with JIA and polyarthritis plus risk factors, should triple non-biologic DMARD versus methotrexate monotherapy as initial therapy be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question in patients with risk factors. However, one open-label clinical trial addressed this question in patients without risk factors (PICO 18) and can be used as indirect evidence for this question.[1] Patients in this trial participated in one of three arms: infliximab + MTX, MTX alone, and MTX+ sulfasalazine + hydroxychloroquine (COMBO). No significant differences were reported for all outcomes including ACR Pedi 75, inactive disease, drug survival, mean state of inactive disease, and CHAQ change at 54 weeks. Three MTX patients were hospitalized for infections.

Quality of evidence across all critical outcomes: Very low

MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Triple DMARD	With MTX		Risk with Triple DMARD	Risk difference with MTX
ACR Pedi 75											
40 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	13/20 (65.0%)	10/20 (50.0%)	**OR 0.54** (0.15 to 1.92)	650 per 1,000	**149 fewer per 1,000** (432 fewer to 131 more)
Inactive Disease											

MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
40 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	8/20 (40.0%)	5/20 (25.0%)	**OR 0.50** (0.13 to 1.93)	400 per 1,000	**150 fewer per 1,000** (320 fewer to 163 more)
Mean State of Inactive Disease (weeks)											
40 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [e]	none	⊕◯◯◯ VERY LOW	20	20	-	-	MD **7 lower** (14.67 lower to 0.67 higher)
CHAQ change at 54 weeks											
40 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	⊕◯◯◯ VERY LOW	20	20	-	-	MD **0.27 lower** (0.55 lower to 0.01 higher)
Serious Adverse Events											
40 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [f]	none	⊕◯◯◯ VERY LOW	0/20 (0.0%)	3/20 (15.0%)	**RR 7.00** (0.38 to 127.32)	0 per 1,000	**Not estimable**

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Open label study

b. Not applicable

c. Only 1 out of 40 patients had a risk factor (RF+)

d. Small study. 95% CI overlaps the line of no difference.

e. Small study. Wide CI overlaps the line of no difference.

f. Small study with very few events.

References

1. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011;70(9):1605-1612.

PICO 28. In children and adolescents with JIA and polyarthritis plus risk factors, should triple non-biologic DMARD versus TNFi as initial therapy be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question. However, one open-label clinical trial addressed this question in patients without risk factors (PICO 18) and can be used as indirect evidence for this question.[1] This study is also indirect in that it does not use a TNFi in isolation; infliximab was always used with the DMARD MTX in this study. Furthermore, only the TNFi infliximab was used to address the question. The data regarding methotrexate alone was excluded from this analysis, as this was not a part of the PICO question. This study directly addressed polyarticular JIA patients, however, it was open label and there was no blinding of participants. The authors found a significantly higher proportion of patients in the TNFi arm achieved an ACR Pedi 75 compared to the COMBO arm (p=0.0005), however the findings were imprecise due to the small number of patients. There was also a significantly higher percentage of patients with inactive disease in the TNF group compared to COMBO (p=0.05). The TNFi group also had a significant higher number of weeks of inactive disease compared to the COMBO counterparts (p=0.044). There were no serious adverse events of interest (in this situation defined as infection requiring hospitalization, hospitalization, malignancy). There was evidence of infection however, with 36 infections identified in the TNF group and 35 in the COMBO group.

Quality of evidence across all critical outcomes: Very low

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Triple DMARD	With TNFi and MTX		Risk with Triple DMARD	Risk difference with TNFi and MTX
ACR Pedi 75											

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
39 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [d]	none	◻◯◯◯ VERY LOW	13/20 (65.0%)	19/19 (100.0%)	**OR 21.67** (1.14 to 412.15)	650 per 1,000	**326 more per 1,000** (29 more to 349 more)
Inactive Disease											
39 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [e]	none	◻◯◯◯ VERY LOW	8/20 (40.0%)	13/19 (68.4%)	**OR 3.25** (0.87 to 12.14)	400 per 1,000	**284 more per 1,000** (33 fewer to 490 more)
Mean State of Inactive Disease (weeks)											
39 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⊕⊕◯◯ LOW	20	19	**Favors TNFi + MTX**	-	MD **13 higher** 2.92 higher to 23.08 higher)
CHAQ change at 54 weeks											

TNFi plus MTX compared to Triple DMARD for patients with polyarticular JIA

Bibliography: Tynjala P et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011; 70(9): 1605-12.

Quality assessment							Summary of findings				
39 (1 RCT)	serious [a]	not serious [b]	serious [c]	serious [e]	none	□◯◯◯ VERY LOW	20	19	-	-	MD **0.1 lower** (0.38 lower to 0.18 higher)
Serious Adverse Events											
40 (1 RCT)	not serious	not serious [b]	serious [c]	very serious [f]	none	□◯◯◯ VERY LOW	0/20 (0.0%)	0/20 (0.0%)	not estimable	0 per 1,000	not estimable

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. open label study

b. not applicable

c. TNFi arm also received MTX, only 1 out of 40 patients had a risk factor (RF+)

d. small study with wide confidence interval

e. confidence interval overlaps the line of no difference

f. sample size too small to rule out serious adverse events

References

1. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011;70(9):1605-1612.

PICO 29. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus TNFi as initial therapy be recommended?

Summary: The literature searches Identified no studies that addressed this question where the majority of patients had risk factors. However, the studies addressing PICO 20 did enroll a small percentage of patients who were RF+ (13-20%). See summary text and findings under PICO 20.

Quality of evidence across all critical outcomes: Very low

References

1. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.
2. Klotsche J, Niewerth M, Haas JP, Huppertz HI, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.
3. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794-2804.

PICO 30. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus abatacept as initial therapy be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 31. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus tocilizumab as initial therapy be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 32. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with TNFi versus tocilizumab as initial therapy be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. However, the observational study by Horneff et al. that was used to address PICO 23 had a small proportion of patients (9-12% across treatment arms) that were RF+. For more information, see the summary text and tables under PICO 23.

Quality of evidence across all critical outcomes: Very low

PICO 33. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with TNFi versus abatacept as initial therapy be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. However, a recent systematic review performed a network meta-analysis of placebo-controlled trials of TNFis and abatacept to indirectly compare treatment efficacy of these medications in patients with JIA. Adalimumab and abatacept showed no significant difference for the outcomes ACR 50 (RR 1.12, 95% CI 0.65 to 1.96) and ACR 70 (RR 1.34, 95% CI 0.65 to 2.79), but the 95% CIs are imprecise. Etanercept and abatacept also showed no significant difference for ACR 50 (RR 2.1, 95% CI 0.95 to 4.64) and ACR 70 (RR 1.31, 95% CI 0.48 to 3.60), but again there was imprecision in the CIs. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. Due to the indirectness of the comparison, population (most patients did not have risk factors) and imprecision in effect estimates, the overall quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

References

1. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess 2016;20(34).

PICO 34. In children and adolescents with JIA and polyarthritis plus risk factors, should initial therapy with abatacept versus tocilizumab as initial therapy be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. However, a recent systematic review performed a network meta-analysis of placebo-controlled trials of tocilizumab and abatacept to indirectly compare treatment efficacy of these

medications in patients with JIA. Abatacept and tocilizumab did not show significant differences in ACR 50 (RR 1.05, 95% CI 0.72 to 1.53) or ACR 70 (RR 1.13, 95% CI 0.66 to 1.93), but the effect estimates were imprecise due to wide 95% CIs. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. Due to the indirectness of the comparison, population (most patients did not have risk factors) and imprecision in effect estimates, the overall quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

References

1. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess 2016;20(34).

PICO 35. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 36. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to triple non-biologic DMARD therapy versus adding TNFi to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 37. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 38. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 39. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) and no risk factors, receiving TNFi, should changing to second drug within same class (TNFi) versus changing to OBRM be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 40. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 41. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to triple non-biologic DMARD therapy versus adding TNFi to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 42. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 43. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 44. In children and adolescents with JIA and polyarthritis with low disease activity (cJADAS < 2.5) plus risk factors, receiving TNFi, should changing to second drug within same class (TNFi) versus changing to OBRM be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 45: In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?

Summary: This PICO was addressed indirectly by three placebo-controlled trials and one open-label, extended-treatment trial[1-5] and by direct drug comparison in one RCT.[6] We supplemented the evidence with data from 8 observational studies evaluating TNFi's, mostly focused on etanercept in polyarthritis patients.[7-14] Most studies did not specifically enroll patients with no risk factors and did not report data separately for patients with no risk factors. In general, all studies included a majority of patients that had no risk factors, and at least one RCT specifically excluded patients who were RF positive (see below).

One RCT directly comparing patients who switched DMARDs to patients adding etanercept to a methotrexate regimen found no significant between-group difference in adverse events or in the proportion of patients achieving ACR 30, 50, 70 or inactive disease, although methotrexate plus etanercept group was favored for adjusted ACR 30/50/70 at 3 months. However, the findings were imprecise due to the low number of patients and wide 95% CIs that crossed the line of no difference (Table 1).[6] This trial specifically excluded patients who were RF positive.

In another RCT, etanercept provided statistically significant improvements over baseline vs. placebo for two outcomes at 7 months (30% improvement over baseline and CHAQ), and non-significant improvements for several outcomes (including active joint count, Physician's Global Assessment of Disease Severity) in 51 methotrexate-resistant polyarticular patients (Table 2).[1] 24-months into the open-label extension trial, 69% of the 51 patients (intent-to-treat group) met the ACR 30, 67% met the ACR 50, and 57% met the ACR 70.[2] Three SAEs (including depression, gastroenteritis-flu syndrome, and sepsis) were reported in these studies. Eight years into this trial, ACR pedi 30/50/70/90/100 response rates were 83%/77%/61%/41%/18%, respectively, and the overall SAE rate remained at 0.12 events/patient-year.[3] These studies may have been underpowered to detect a between-group difference.

Additional efficacy data from observational studies evaluating etanercept (see Table 5) included:

- At 3 months, 45/232 (19.3%) non-systemic JIA patients with moderately high-to-high disease activity achieved inactive disease.[9]
- At 12 months, ACR Pedi 30: 74%; ACR Pedi 50: 69%; ACR Pedi 70: 56%; and ACR Pedi 90: 38%.[7]
- At 15 months, 58/232 (25%) non-systemic JIA patients with moderately high-to-high disease activity achieved inactive disease.[9]
- At 24 months, all efficacy outcomes showed significant improvements over baseline. 96.5% achieved ACR 30, 93.8% achieved ACR 50, and 90.3% achieved ACR 70.[13]
- At 27 months and 39 months, ACR70 for non-systemic JIA was 58% and 25%.[14]
- At median 28 months, 41.8% achieved inactive disease by Wallace criteria.[8]

- At 5 years, 26% were rated by physicians as having inactive disease. 19% were rated as having inactive disease or remission on medication (per Wallace criteria). 6% were rated as being in clinical remission off medication. 24% of patient's rated themselves as having inactive disease.[12]

Additional safety data from observational studies evaluating etanercept (see Table 5) included:

- SAE rate of 0.029 per patient year. IBD (n=2) and sarcoidosis (n=2) occurred in patients with no prior symptoms of either disorder.[14]
- SAE rate of 5.7 per 100 patient-years. Serious infection rate of 1.7 per 100 patient-years. Rate of de novo autoimmune events was 1.5 per 100 patient-years.[12]
- New or recurrent uveitis (n=38), inflammatory bowel disease (n=10), death from fulminant Strep bacteremia with pneumonia (n=1), tuberculosis (n=1), malignancies (n=2).[8]

Another RCT with a less direct comparison found that adalimumab plus methotrexate was superior to methotrexate alone regarding the proportion of patients achieving ACR 30/50/70 at 3 months (Table 3).[4]

One observational study evaluating adalimumab in biologic naïve (n=130) or biologic switchers (n=159) reported higher 6 month ACR 30/50/70/90 responses in biologic naïve patients.[10] Lastly, 10-year followup of one trial showed rates of SAE for various TNFis including: 11.4/100 patient years on etanercept, 11.8 on infliximab, 10.1 on adalimumab, 15.7 on abatacept, 31.2 on tocilizumab and 87.5 on rituximab, higher than with most anti-TNF agents (P = 0.005). The occurrence of serious infectious AEs on rituximab (37.5/100 py) was greater than on all other anti-TNFs (RR 6.16, 95% CI 1.59 to 23.8; p = 0.008).[10]

In part 2 (weeks 16-48) of a 3-part trial, Golimumab did not provide any statistically significant benefit vs. placebo for efficacy or safety outcomes for 154 patients randomized after a 16-week open-label, lead-in period (part 1) in which patients received subcutaneous golimumab every 4 weeks (Table 4).[5]

Quality of evidence across all critical outcomes: Low

Table 1. MTZ/SSZ compared to MTX plus ETN in poly JIA

Bibliography: Hissink Muller PC, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017;15(1):11.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. MTZ/SSZ compared to MTX plus ETN in poly JIA

Bibliography: Hissink Muller PC, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017;15(1):11.

Quality assessment							Summary of findings				
(studies) Follow-up	bias					evidence	With MTX plus ETAN	With MTZ/SSZ	(95% CI)	Risk with MTX plus ETAN	Risk difference with MTZ/SSZ
Inactive disease											
62 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	5/30 (16.7%)	8/32 (25.0%)	**RR 1.50** (0.55 to 4.08)	167 per 1,000	**83 more per 1,000** (75 fewer to 513 more)
adjusted ACR 30, 3 mo											
62 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	22/30 (73.3%)	16/32 (50.0%)	**RR 0.68** (0.45 to 1.03)	733 per 1,000	**235 fewer per 1,000** (403 fewer to 22 more)
adjusted ACR 50, 3 mo											
62 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	16/30 (53.3%)	10/32 (31.3%)	**RR 0.59** (0.32 to 1.08)	533 per 1,000	**219 fewer per 1,000** (363 fewer to 43 more)
adjusted ACR 70, 3 mo											

Table 1. MTZ/SSZ compared to MTX plus ETN in poly JIA

Bibliography: Hissink Muller PC, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017;15(1):11.

Quality assessment							Summary of findings				
62 (1 RCT)	not serious	not serious [a]	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	14/30 (46.7%)	8/32 (25.0%)	**RR 0.54** (0.26 to 1.09)	467 per 1,000	**215 fewer per 1,000** (345 fewer to 42 more)
Viral pneumonia											
62 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	0/30 (0.0%)	1/32 (3.1%)	**OR 2.90** (0.11 to 74.10)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Prolonged vomiting											
62 (1 RCT)	not serious	not serious [a]	not serious	serious [c]	none	⊕⊕⊕◯ MODERATE	0/30 (0.0%)	1/32 (3.1%)	**OR 2.90** (0.11 to 74.10)	0 per 1,000	**Not calculable**

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Not applicable

b. Small study. 95% CI includes the possibility of no difference.

c. Small study with only 1 event. Wide 95% CI that overlaps the line of no difference.

Table 2. Etanercept compared to placebo in polyarticular JIA

Bibliography: Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With ETN		Risk with placebo	Risk difference with ETN
Active joint count (median), 7 mos											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	13/26 (50.0%)	7/25 (28.0%)	**OR 0.39** (0.12 to 1.24)	500 per 1,000	**219 fewer per 1,000** (393 fewer to 54 more)
Joints with limitation of motion (median), 7 mos											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	5/26 (19.2%)	1/25 (4.0%)	**OR 0.17** (0.02 to 1.62)	192 per 1,000	**153 fewer per 1,000** (188 fewer to 86 more)
Improvement (30% over baseline), 7 mos											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	9/26 (34.6%)	20/25 (80.0%)	**OR 7.56** (2.12 to 26.91) **Favors ETN**	346 per 1,000	**454 more per 1,000** (183 more to 588 more)
Depression/personality disorder											

Table 2. Etanercept compared to placebo in polyarticular JIA

Bibliography: Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.

Quality assessment							Summary of findings				
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/26 (0.0%)	1/25 (4.0%)	**OR 3.24** (0.13 to 83.47)	0 per 1,000	**Not calculable**
Gastroenteritis-flu syndrome											
51 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	0/26 (0.0%)	1/25 (4.0%)	**OR 3.24** (0.13 to 83.47)	0 per 1,000	**Not calculable**

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison

c. Small single study. 95% CI includes the possibility of no difference.

d. Small single study.

e. Small single study with only 1 event. Very wide 95% CI that overlaps the line of no difference.

Table 3. Adalimimab + MTX compared to MTX in poly JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Certainty assessment							Summary of findings		
№ of participants	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Study event rates (%)**	**Relative effect**	**Anticipated absolute effects**

Table 3. Adalimimab + MTX compared to MTX in poly JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Certainty assessment							Summary of findings				
(studies) Follow-up	bias					of evidence	With MTX	With Adalimimab + MTX	(95% CI)	Risk with MTX	Risk difference with Adalimimab + MTX
ACR 30											
75 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	14/37 (37.8%)	24/38 (63.2%)	**OR 2.82** (1.10 to 7.18) **Favors ADA + MTX**	378 per 1,000	**254 more per 1,000** (23 more to 435 more)
ACR 50											
73 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	14/37 (37.8%)	24/36 (66.7%)	**OR 3.29** (1.26 to 8.58) **Favors ADA + MTX**	378 per 1,000	**289 more per 1,000** (56 more to 461 more)
ACR 70											
75 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	10/37 (27.0%)	24/38 (63.2%)	**OR 4.63** (1.74 to 12.34) **Favors ADA + MTX**	270 per 1,000	**361 more per 1,000** (122 more to 550 more)

Table 3. Adalimimab + MTX compared to MTX in poly JIA

Bibliography: Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.

Certainty assessment							Summary of findings				
ACR 90											
75 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	10/37 (27.0%)	16/38 (42.1%)	**OR 1.96** (0.74 to 5.18)	270 per 1,000	**150 more per 1,000** (55 fewer to 387 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison

c. Small single study. Wide 95% CI includes the line of no difference.

Table 4. Golimumab compared to placebo in poly JIA

Bibliography: Brunner HI, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2017.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Golimumab**		**Risk with placebo**	**Risk difference with Golimumab**
Clinical remission, 48 weeks											

Table 4. Golimumab compared to placebo in poly JIA

Bibliography: Brunner HI, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2017.

Quality assessment							Summary of findings				
153 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/75 (12.0%)	10/78 (12.8%)	**RR 1.07** (0.46 to 2.48)	120 per 1,000	**8 more per 1,000** (65 fewer to 178 more)
ACR 30, 48 weeks											
153 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	41/75 (54.7%)	41/78 (52.6%)	**RR 0.96** (0.72 to 1.29) **No difference**	547 per 1,000	**22 fewer per 1,000** (153 fewer to 159 more)
ACR 50, 48 weeks											
153 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	40/75 (53.3%)	40/78 (51.3%)	**RR 0.96** (0.71 to 1.30) **No difference**	533 per 1,000	**21 fewer per 1,000** (155 fewer to 160 more)
ACR 70, 48 weeks											
153 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	36/75 (48.0%)	37/78 (47.4%)	**RR 0.99** (0.71 to 1.38)	480 per 1,000	**5 fewer per 1,000** (139 fewer to 182 more)
ACR 90, 48 weeks											

Table 4. Golimumab compared to placebo in poly JIA

Bibliography: Brunner HI, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2017.

Quality assessment							Summary of findings				
153 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	24/75 (32.0%)	30/78 (38.5%)	**RR 1.20** (0.78 to 1.85)	320 per 1,000	**64 more per 1,000** (70 fewer to 272 more)
Pneumonia											
154 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	1/76 (1.3%)	0/78 (0.0%)	**RR 0.32** (0.01 to 7.85)	13 per 1,000	**9 fewer per 1,000** (13 fewer to 90 more)
Upper respiratory tract infection											
154 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	1/76 (1.3%)	0/78 (0.0%)	**RR 0.32** (0.01 to 7.85)	13 per 1,000	**9 fewer per 1,000** (13 fewer to 90 more)
Serious adverse events											
154 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	10/76 (13.2%)	8/78 (10.3%)	**RR 0.78** (0.33 to 1.87)	132 per 1,000	**29 fewer per 1,000** (88 fewer to 114 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Not applicable

b. Indirect comparison

c. Single study. 95% CI includes the possibility of no difference.

d. Single study. Wide 95% CI which includes the possibility of no difference.

Table 5. Additional Data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Brunner, 2017[5]	RCT	48 weeks	153 patients with polyarticular JIA	Golimumab: n=78 Placebo: n=75	Mean change in JADAS71-ESR was similar at week 48 (mean change -21 in both groups, estimated Figure 3C)
Hissink Muller, 2017[6]	RCT	3 months	62 patients with polyarticular JIA	Sequential MTX/SSZ: n=32 MTX plus Etanercept: n=30	Median change in JADAS-10 at 3 months was higher for MTX plus Etanercept (6.9 sequential, 10.2 MTX plus Etanercept)
Kearsley-Fleet, 2016[7]	Cohort	2004-2014 ETN as first biologic with records available for baseline and year 1 visit	496 severe JIA patients, ~60% polyarticular	Etanercept for 1 year or stopped due to remission	At 1 year, ACR Pedi 30: 74%; ACR Pedi 50: 69%; ACR Pedi 70: 56%; and ACR Pedi 90: 38%. <u>Median (IQR) at 1 year</u> Active joint count (n=451): 0.0 (0.0-2.0) Physician global (n=344): 0.9 (0.0-2.0) Parent/patient global (n=349): 1.3 (0.2-3.9) CHAQ (n=341): 0.4 (0.0-1.1) ESR (n=345): 7.0 (4.0-17.0) CRP (n=348): 5.0 (3.0-7.0) JADAS-71: 3.8 (0.8-9.0)
Verazza, 2016[8]	Survey	Median (IQR) followup 2.4 years (0.7-6.3)	422 polyarticular JIA patients still taking Etanercept	Etanercept (ETN) Median duration of ETN: 2.5 years	41.8% achieved inactive disease by Wallace criteria (51% by Wallace without ESR/CRP; 48.6% achieved inactive disease measured by cJADAS10, 46.4% achieved inactive disease measured by JADAS10.) 68.5% had no active joints. 60% had no restricted joints. 56.6% achieved Physician's VAS as 0. 80.7% had an ESR <20 mm/h. 84.8% had a normal CRP. New or recurrent uveitis: 38

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Death from fulminant Strep bacteremia with pneumonia: 1 Tuberculosis: 1 Malignancies (bladder and thyroid carcinoma): n=2 Inflammatory bowel diseases : 10
Otten, 2015[9]	Cohort	12 years over 1999 and 2010	335 patients with non-systemic JIA, 86 systemic JIA	Etanercept 90% started ETN, 9% started adalimumab	At 3 months, 45/232 (19.3%) non-systemic JIA patients with moderately high-to-high disease activity achieved inactive disease. At 15 months, 58/232 (25%) non-systemic JIA patients with moderately high-to-high disease activity achieved inactive disease. At 3 and 15 months, median JADAS-10 scores decreased non-significantly for non-systemic JIA patients.
Tarkiainen, 2015[10]	Cohort	10 years	348 patients with JIA, JIA-associated uveitis or chronic anterior uveitis without arthritis	Out of 1516 patient-years (py) included: 710 on etanercept, 591 on infliximab, 188 on adalimumab, 8 on rituximab, 5 on anakinra, 6 on tocilizumab, 6 on abatacept and 1 on golimumab.	121 patients (35%) experienced SAEs (173 events; 11.4/100 py). Serious infections: 44 patients (12.6%) 21 on ETN (4.2/100 py), 19 on IFX (3.4/100 py), 3 on ADA (2.1/100 py) and 1 (97.5/100 py) on GLM. Rate of SAEs was 11.4/100 py on etanercept, 11.8 on infliximab, 10.1 on adalimumab, 15.7 on abatacept, 31.2 on tocilizumab and 87.5 on rituximab, higher than with most anti-TNF agents (P = 0.005). The occurrence of serious infectious AEs on RTX (37.5/100 py) was greater than on all other anti-TNFs (RR 6.16, 95% CI 1.59 to 23.8; p = 0.008).
Schmeling, 2014[11]	Cohort	1 year	289 JIA patients; 130 biologic naïve JIA, 159 biologic switcher JIA	Adalimumab 24mg/m^2 (max dose 40mg) every other week	6 Month Pedi ACR in biologic naïve: ACR 30: 63.4% ACR 50: 61.0% ACR 70: 48.8% ACR 90: 34.2% 6 Month Pedi ACR in biologic switcher: ACR 30: 47.6% ACR 50: 38.1% ACR 70: 21.9% ACR 90: 15.2%

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					11 SAEs were reported (2.5 per 100 patient-years); 6 in biologic naïve, 5 in biologic switcher. SAEs per 100 patient-years: 2.5 (95% CI: 1.4–4.6) Infectious SAEs per 100 patient-years: 0.2 (95% CI: 0 to 1.6) Crohn's disease: 1 Intestinal resection: 1 Diabetes mellitus: 1
Minden, 2012[12]	Cohort	2007 to 2010 All patients had received Etanercept for an average of almost 5 years, with a maximum of 10 years.	346 adult patients diagnosed with JIA in childhood (mostly polyarticular) AND who received Enbrel during childhood AND who were assessed at least once in the JUMBO registry	Etanercept (Enbrel; no specific dose or duration of treatment required for entry)	Median (IQR) score for Physician Rating of Disease Activity (NRS 0-10): 1 (0 to 2). 26% rated by physicians as having inactive disease (NRS=0). 19% rated as having inactive disease or remission on medication (per Wallace criteria). 6% rated as being in clinical remission off medication. 24% of patients rated themselves as having inactive disease (NRS=0). Serious adverse event rate for patients on ETN: 5.7 per 100 patient-years. Serious infection rate of 1.7 per 100 patient-years (10 infections) for patients on ETN. Rate of de novo autoimmune events was 1.5 per 100 patient-years for patients on ETN.
Halbig and Horneff, 2009[13]	Cohort	2001-2006 (June 1st)	437 JIA patients (~60% polyarticular) 114 met inclusion criteria (complete data, continuous	Etanercept (Enbrel; no specific dose or duration of treatment required for entry) 82% had concomitant MTX treatment	At 24 months followup, 96.5% achieved ACR 30, 93.8% achieved ACR 50, and 90.3% achieved ACR 70. At 24 months, significant improvements (p<0.0001) in number of active joints vs. baseline: 3±6. At 24 months, significant improvements (p<0.0001) in Physician's Global

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			treatment for 24 months) Data collected at start of etanercept and reassessed every 6 months		Assessment of the Overall Disease Activity (p<0.0001) vs. baseline: 1.5±2. At 24 months, significant improvements (p<0.0001) in ESR (mm/h) vs. baseline: 14±12. At 24 months, significant improvements (p<0.0001) in CRP (mg/l) vs. baseline: 8.8±15.7 At 24 months, significant improvements (p<0.0001) in Patient's Assessment of Overall Well Being vs. baseline: 1.4±1.7 At 24 months, significant improvements (p<0.0001) in CHAQ DI vs. baseline: 0.34±0.52.
Prince, 2009[14]	Cohort	Median 2.5 years per patient	146 JIA patients, 65% polyarticular	Etanercept. Most patients received etanercept at the usual dose of 0.4 mg/kg twice weekly; in 28 patients etanercept was initiated or changed to a double dose of 0.8 mg/kg once weekly. Median duration of etanercept therapy was 1.7 years (range 0.1 to 6.8 years).	The ACR 30 for non-sJIA at 3, 15, 27, and 39 months was 84%, 85%, 70%, and 37%. ACR50 for non-sJIA at 3, 15, 27, and 39 months was 74%, 84%, 63%, and 32%. ACR70 for non-sJIA at 3, 15, 27, and 39 months was 58%, 71%, 58%, and 25%. Serious adverse events occurred in 9 patients with an SAE rate of 0.029 per patient year. IBD occurred in 2 patients, and sarcoidosis occurred in 2 patients with no prior symptoms of either disorder.
Lovell, 2002[2], 2008[3]	Open-label, extended - treatment trial (primary trial [1])	24 months	43 MTX-resistant JIA patients, 51 MTX-resistant JIA patients in modified ITT	Etanercept was administered at a dosage of 0.4 mg/kg (maximum 25 mg) subcutaneously twice each week	Two years into this extension trial, 69% of the 51 patients (ITT group) met the ACR 30, 67% met the ACR 50, and 57% met the ACR 70. 1 patient who was taking ETN for more than 2 years had SAE (sepsis). 8 years into the extension trial, the overall SAE rate remained at 0.12 events/patient-year. ITT analysis found ACR pedi 30/50/70/90/100 response rates of 83%/77%/61%/41%/18%.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Lovell, 2000[1]	RCT	7 months	51 patients with polyarticular JIA	Etanercept: n=25 Placebo: n=26	Median score for Physician's Global Assessment of Disease Severity at 7 months worse for placebo (5 placebo, 2 Etanercept) Median score for Patient's or Parent's Global Assessment of Overall Well-being at 7 months worse for placebo (5 placebo, 3 Etanercept). Median score for CHAQ worse at 7 months for placebo (1.2 placebo, 0.8 Etanercept). Median improvement over baseline significantly higher for Etanercept (0% placebo, 54% Etanercept; p=0.01). Median score for ESR (mm/hr) at 7 months worse for placebo (30 placebo, 18 Etanercept). Median score for CRP (mg/dl) at 7 months worse for placebo (3.0 placebo, 0.4 Etanercept).[normal range 0 to 0.79]

JADAS71-ESR: Juvenile Arthritis Disease Activity Score using erythrocyte sedimentation rate; **RR**: relative risk

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PICO 46: In children and adolescents with JIA and polyarthritis with moderate/ high disease activity (cJADAS > 2.51), no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD or adding abatacept to original non-biologic DMARD be recommended?

Summary: Literature searches revealed three studies (2 RCTs and 1 open label extension) which seemed to indirectly address the PICO question (patients in the placebo arm receiving non-biologic DMARD did not switch to a second non-biologic DMARD). Of the two RCTs, however, the data from one study[1] was not abstracted as both studies[1,2] included the same study population (both part of the AWAKEN trial). Ruperto 2008[2] included data from patients who dropped out in addition to those who remained in the study, while the other study[1] only analyzed those patients who remained in the study and thus was not a good representation of treatment efficacy. Ruperto[2] demonstrated that patients on abatacept significantly improved in terms of their number of active joints, number of joints with limited ROM, physician's global assessment, and CHAQ disability index compared to placebo (Table 1). The measurement for the disability index was imprecise, however, the remaining measurements remained significant. There was also a significantly higher number of patients in the abatacept group vs. placebo group who achieved an ACR Pedi 50/70/90 compared to controls. The difference in ACR Pedi 30 was not significant. There was no statistically significant difference in terms of serious adverse events between the groups. This study was an indirect representation of the PICO question as it compared abatacept to placebo (74% of patients were also receiving methotrexate in both groups) but not abatacept to a second DMARD. In addition, the study population included more than just polyarticular JIA patients. There was also no delineation between patients with risk factors and without which makes this indirect as the PICO question asked specifically about poly-JIA patients without risk factors.

An open-label extension study[3,4] investigated improvement in patients from the initial AWAKEN trial over time (Table 2). As such, the same limitations about the indirectness of the population studied apply here. Researchers found that 19.6% of patients reported experiencing a serious adverse event by the end of the long-term extension period (up to 7 years). The majority of patients (85%) achieved an ACR 30. 43% were found to achieve an ACR 90. Authors concluded that patients on abatacept overall achieved clinically meaningful responses over the long-term (21 months). However, these numbers dropped to 35% and 20.5% in an intention-to-treat analysis that assumed any dropouts or patients with missing data were non-responders.

Quality of evidence across all critical outcomes: Low

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population
Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
(studies) Follow-up	**bias**					**evidence**	**With Placebo end of 6 month period**	**With Abatacept**	**(95% CI)**	**Risk with Placebo end of 6 month period**	**Risk difference with Abatacept**
Number of joints with active arthritis											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	62	60	**Favors abatacept**	-	MD **3.1 lower** (0.93 lower to 5.27 lower)
Physician Global Assessment of child's well being (VAS)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	62	60	**Favors abatacept**	-	MD **11.9 lower** (5.58 lower to 18.22 lower)
Parent global assessment of child's overall well being (VAS)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **6.1 lower** (13.12 lower to 0.92 higher)
CHAQ disability index											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **0.1 lower** (0.37 lower to 0.17 higher)
ESR (mm/hr)											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⊕⊕◯◯ LOW	62	60	-	-	MD **4.7 lower** (13.94 lower to 4.54 higher)
CRP (mg/dL)											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	62	60	-		MD **0.12 lower** (0.25 lower to 0.01 higher)
Improvement, achievement of ACR 30											
122 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	43/62 (69.4%)	49/60 (81.7%)	**RR 1.18** (0.96 to 1.44)	694 per 1,000	**125 more per 1,000** (28 fewer to 305 more)
ACR 50											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	32/62 (51.6%)	46/60 (76.7%)	**RR 1.49** (1.12 to 1.96) **Favors abatacept**	516 per 1,000	**253 more per 1,000** (62 more to 495 more)
ACR 70											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	19/62 (30.6%)	32/60 (53.3%)	**RR 1.74** (1.12 to 2.71) **Favors abatacept**	306 per 1,000	**227 more per 1,000** (37 more to 524 more)
ACR 90											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	10/62 (16.1%)	24/60 (40.0%)	**RR 2.48** (1.30 to 4.73) **Favors abatacept**	161 per 1,000	**239 more per 1,000** (48 more to 602 more)
Inactive disease											
122 (1 RCT)	not serious	not serious [a]	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	7/62 (11.3%)	18/60 (30.0%)	**RR 2.66** (1.20 to 5.90) **Favors abatacept**	113 per 1,000	**187 more per 1,000** (23 more to 553 more)
Total serious adverse events											

Table 1. Abatacept compared to Placebo end of 6 month period for health problem or population

Bibliography: Ruperto N, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (London, England) 2008; 372(9636): 383-91.

Quality assessment							Summary of findings				
252 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	2/62 (3.2%)	6/190 (3.2%)	**RR 0.98** (0.20 to 4.73)	32 per 1,000	**1 fewer per 1,000** (26 fewer to 120 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. not applicable

b. study compares abatacept to placebo but not to second DMARD as asked in the PICO question

c. Confidence interval wide and includes line of no difference

d. Confidence interval crosses the line of no difference

Table 2. Long-term Open Label Extension Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ruperto 2010[3]	Long term open label extension of RCT	All patients had received treatment for at least 21 months	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (data from 120 patients) ACR 30: 103/120 (85.83%) ACR 50: 98/120 (81.67%) ACR 70: 83/120 (69.17%) ACR 90: 52/120 (43.33%) ACR 100: 30/120 (25%) SAE: 23/153 (15.03%) patients reported a SAE
Lovell 2015[4]	Long term open label	Patients had received	153 patients age 6-17	Abatacept 10mg/kg every 28 days	Pedi ACR at end of LTE (Intention-to-treat data from 190 patients, assuming dropouts and patients with missing data were non-

	extension of RCT	treatment for up to 7 years			responders) ACR 30: 35.3% (95% CI 28.5–42.1%) ACR 50: 33.7% (95% CI 27.0–40.4%) ACR 70: 27.4% (95% CI 21.0–33.7%) ACR 90: 20.5% (95% CI 14.8–26.3%) ACR 100: 16.3% (95% CI 11.1–21.6%) SAE: 30/153 (19.6%) patients reported a SAE

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4. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety, efficacy and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arth Rheum 2015; 67(10):2759-2770.

PICO 47. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS > 2.51) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?

Summary: This PICO was addressed by one RCT in an indirect comparison.[1] Among other comparisons, the study compared patients receiving tocilizumab plus methotrexate versus methotrexate monotherapy, but these latter patients had not been switched to a new DMARD (they had been receiving methotrexate previously). Results show a statistically significant difference favoring tocilizumab plus methotrexate versus methotrexate monotherapy for JIA ACR 70, and JIA ACR 90 at 40 weeks (Table 1). Of the 188 patients enrolled in the open-label tocilizumab part of the study, one patient had a positive anti-tocilizumab antibody assay and withdrew from the study due to lack of efficacy.

Overall quality of evidence across all critical outcomes: Low

Table1: MTX compared to Tocilizumab plus MTX for polyarticular JIA

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Tocilizumab plus MTX	With MTX		Risk with Tocilizumab plus MTX	Risk difference with MTX
ACR70, week 40											
131 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	45/67 (67.2%)	30/64 (46.9%)	**RR 0.70** (0.51 to 0.95) **Favors Tocilizumab plus MTX**	672 per 1,000	**201 fewer per 1,000** (329 fewer to 34 fewer)
ACR90, week 40											

Table1: MTX compared to Tocilizumab plus MTX for polyarticular JIA

Bibliography: Brunner HI, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

Quality assessment							Summary of findings				
131 (1 RCT)	serious [a]	not serious [b]	serious [c]	not serious	none	⊕⊕◯◯ LOW	32/67 (47.8%)	18/64 (28.1%)	**RR 0.59** (0.37 to 0.94) **Favors Tocilizumab plus MTX**	478 per 1,000	**196 fewer per 1,000** (301 fewer to 29 fewer)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Randomization, allocation, and blinding not mentioned

b. Not applicable

c. Indirect treatment comparison

References

1. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

PICO 48. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) and no risk factors, receiving TNFi (+/-non-biologic DMARD), should changing to second drug within same class (TNFi) versus changing to different drug in different OBRM class be recommended?

Summary: This PICO was addressed by one observational study direct drug comparison[1] and one longitudinal observational study looking at adalimumab in biologic naïve vs biologic switchers[2]. Results for the direct drug comparisons between tocilizumab vs. adalimumab (Table 1), tocilizumab vs. etanercept (Table 2) and etanercept vs. adalimumab (Table 3) show no statistically significant differences in JADAS10, JIA ACR 30/50/70/90, and reduction in CHAQ-DI. When comparing SAE, there was no statistically significant difference between tocilizumab and adalimumab, but the tocilizumab group had significantly fewer events than the etanercept group. In the adalimumab vs etanercept comparison, the adalimumab group had significantly fewer events than the etanercept group. In the longitudinal observational study with adalimumab treatment, biologic naïve patients appear to have greater efficacy compared to biologic switchers in JIA ACR 30/50/70/90 (Table 4). There does not appear to be any difference between the groups in regards to SAE.

Overall quality of evidence across all critical outcomes: Very low

Table 1. Tocilizumab compared to ADA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With ADA	With Tocilizumab		Risk with ADA	Risk difference with Tocilizumab
JADAS10											
310 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	236	74	-	-	MD **2.2 lower** (6.04 lower to 1.64 higher)
ACR 30 at 3 months											

Table 1. Tocilizumab compared to ADA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
310 (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	158/236 (66.9%)	45/74 (60.8%)	**RR 0.91** (0.74 to 1.11) **No difference**	669 per 1,000	**60 fewer per 1,000** (174 fewer to 74 more)
ACR 50 at 3 months											
310 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	139/236 (58.9%)	38/74 (51.4%)	**RR 0.87** (0.68 to 1.12)	589 per 1,000	**77 fewer per 1,000** (188 fewer to 71 more)
ACR 70 at 3 months											
310 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	101/236 (42.8%)	26/74 (35.1%)	**RR 0.82** (0.58 to 1.16)	428 per 1,000	**77 fewer per 1,000** (180 fewer to 68 more)
ACR 90 at 3 months											
310 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	64/236 (27.1%)	19/74 (25.7%)	**RR 0.95** (0.61 to 1.47)	271 per 1,000	**14 fewer per 1,000** (106 fewer to 127 more)
Reduction in CHAQ-DI											

Table 1. Tocilizumab compared to ADA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
310 (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	236	74	-	The mean reduction in CHAQ-DI was **0**	MD **0.19 higher** (0.07 higher to 0.31 higher)
SAE											
310 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	26/236 (11.0%)	3/74 (4.1%)	**RR 0.37** (0.11 to 1.18)	110 per 1,000	**69 fewer per 1,000** (98 fewer to 20 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. No randomization, allocation concealment or blinding. Retrospective study with high risk of selection bias.

b. C.I. crosses no effect line

Table 2. Tocilizumab compared to ETA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ETA	**With Tocilizumab**		**Risk with ETA**	**Risk difference with Tocilizumab**
JADAS10											
493 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	419	74	-	-	MD **3.5 lower** (7.15 lower to 0.15 higher)
ACR 30 at 3 months											
493 (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	285/419 (68.0%)	45/74 (60.8%)	**RR 0.89** (0.74 to 1.09) **No difference**	680 per 1,000	**75 fewer per 1,000** (177 fewer to 61 more)
ACR 50 at 3 months											
493 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	251/419 (59.9%)	38/74 (51.4%)	**RR 0.86** (0.68 to 1.08)	599 per 1,000	**84 fewer per 1,000** (192 fewer to 48 more)
ACR 70 at 3 months											

Table 2. Tocilizumab compared to ETA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
493 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	176/419 (42.0%)	26/74 (35.1%)	**RR 0.84** (0.60 to 1.16)	420 per 1,000	**67 fewer per 1,000** (168 fewer to 67 more)
ACR 90 at 3 months											
493 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	101/419 (24.1%)	19/74 (25.7%)	**RR 1.07** (0.70 to 1.63)	241 per 1,000	**17 more per 1,000** (72 fewer to 152 more)
Reduction in CHAQ-DI											
493 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	419	74	-	-	MD **0.09 higher** (0.03 lower to 0.21 higher)
SAE											
493 (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	119/419 (28.4%)	3/74 (4.1%)	**RR 0.14** (0.05 to 0.44) **Favors tocilizumab**	284 per 1,000	**244 fewer per 1,000** (270 fewer to 159 fewer)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. No randomization, allocation concealment, or blinding. Retrospective study with high risk of selection bias.

b. C.I. crosses no effect line

Table 3. ETA compared to ADA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ADA	**With ETA**		**Risk with ADA**	**Risk difference with ETA**
JADAS10											
655 (1 observational study)	very serious [a]	not serious	serious [c]	serious [b]	none	⨁◯◯◯ VERY LOW	236	419	-	-	MD **1.3 higher** (0.27 lower to 2.87 higher)
ACR 30 at 3 months											
655 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	158/236 (66.9%)	285/419 (68.0%)	**RR 1.02** (0.91 to 1.14) **No difference**	669 per 1,000	**13 more per 1,000** (60 fewer to 94 more)
ACR 50 at 3 months											
655 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	139/236 (58.9%)	251/419 (59.9%)	**RR 1.02** (0.89 to 1.16) **No difference**	589 per 1,000	**12 more per 1,000** (65 fewer to 94 more)
ACR 70 at 3 months											

Table 3. ETA compared to ADA for Polyarthritic JIA

Bibliography: Horneff G, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

Quality assessment							Summary of findings				
655 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	101/236 (42.8%)	176/419 (42.0%)	**RR 0.98** (0.82 to 1.18) **No difference**	428 per 1,000	**9 fewer per 1,000** (77 fewer to 77 more)
ACR 90 at 3 months											
655 (1 observational study)	very serious [a]	not serious	serious [c]	serious [b]	none	⨁◯◯◯ VERY LOW	64/236 (27.1%)	101/419 (24.1%)	**RR 0.89** (0.68 to 1.16)	271 per 1,000	**30 fewer per 1,000** (87 fewer to 43 more)
Reduction in CHAQ-DI											
655 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	236	419	-	The mean reduction in CHAQ-DI was **0**	MD **0.1 higher** (0.02 higher to 0.18 higher)
SAE											
655 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	26/236 (11.0%)	119/419 (28.4%)	**RR 2.58** (1.74 to 3.82) **Favors Ada**	110 per 1,000	**174 more per 1,000** (82 more to 311 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. No randomization, allocation concealment, or blinding. Retrospective study with high risk of selection bias.

b. C.I. crosses no effect line

c. Compares two TNFis, no comparison to switching to other OBRM

Table 4. Adalimumab in Biologic Naïve versus Biologic Switchers

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1376 Schmeling 2014 [2]	Longitudinal multicenter observational study	1 year	130 biologic naïve JIA 159 biologic switcher JIA	Adalimumab 24mg/m^2 (max dose 40mg) every other week	6 Month Pedi ACR in biologic naïve: ACR 30: 63.4% ACR 50: 61.0% ACR 70: 48.8% ACR 90: 34.2% 6 Month Pedi ACR in biologic switcher: ACR 30: 47.6% ACR 50: 38.1% ACR 70: 21.9% ACR 90: 15.2% SAE in biologic naïve: 6/130 SAE in biologic switcher: 5/159

References

1. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.
2. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol. 2014;66(9):2580-2589.

PICO 49: In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) and no risk factors, should rituximab versus 3rd class OBRM approved for JIA be recommended?

Summary. The literature searches identified one retrospective study that addressed this question.[1] The only relevant outcomes reported were serious adverse events; in general, rituximab had higher rates of serious adverse events than tocilizumab or TNF inhibitors (see results in Table below).

Overall quality of evidence across all critical outcomes. Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Tarkiainen M., 2015 [1]	Retrospective observational study	10 years	348 patients with JIA. A total of 19 patients (5.5%) had systemic-onset JIA, 30 (8.6%) had persistent and 65 (18.7%) extended oligoarthritis, 175 (50.3%) had RF-negative and 16 (4.6%) RF-positive polyarthritis, 10 (2.9%) had psoriatic and 22 (6.3%) enthesitis-related arthritis, 1 (0.3%) was unclassified and 10 (2.9%) had uveitis only.	Out of 1516 patient-years (py) included: 710 on etanercept, 591 on infliximab, 188 on adalimumab, 8 on rituximab, 5 on anakinra, 6 on tocilizumab, 6 on abatacept and 1 on golimumab.	121 patients (35%) experienced serious AEs (173 events; 11.4/100 py). Rate of serious AEs was 11.4/100 py on etanercept, 11.8 on infliximab, 10.1 on adalimumab, 15.7 on abatacept, 31.2 on tocilizumab and 87.5 on rituximab, higher than with most anti-TNF agents (P = 0.005). Serious infections: 44 patients (12.6%) 21 on ETN (4.2/100 py), 19 on IFX (3.4/100 py), 3 on ADA (2.1/100 py) and 1 (97.5/100 py) on GLM. The occurrence of serious infectious AEs on RTX (37.5/100 py) was greater than on all other anti-TNFs (RR 6.16, 95% CI 1.59 to 23.8; p = 0.008).

References:

1. Tarkiainen M. et al., Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. 2014, Rheumatology 2015;54:11701176, doi:10.1093/rheumatology/keu457

PICO 50. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) plus risk factors, receiving non-biologic DMARD monotherapy, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. Most of the studies in the evidence base for PICO 45 included a minority of patients with risk factors, and therefore provide indirect evidence for PICO 50. However, the RCT by Hissink Muller (PICO 45, Table 1) specifically excluded patients with risk factors, so all of the outcomes graded as Moderate in that table should be downgraded to Low with respect to PICO 50. For more information see the text summary and tables under PICO 45.

Quality of evidence across all critical outcomes: Very low

References

1. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-769.
2. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum. 2003;48(1):218-226.
3. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 2008;58(5):1496-1504.
4. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810-820.
5. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2017.
6. Hissink Muller PC, Brinkman DM, Schonenberg D, Koopman-Keemink Y, Brederije IC, Bekkering WP, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017;15(1):11.
7. Kearsley-Fleet L, Davies R, Lunt M, Southwood TR, Hyrich KL. Factors associated with improvement in disease activity following initiation of etanercept in children and young people with Juvenile Idiopathic Arthritis: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Rheumatology (Oxford). 2016;55(5):840-847.
8. Verazza S, Davi S, Consolaro A, Bovis F, Insalaco A, Magni-Manzoni S, et al. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. Pediatr Rheumatol Online J. 2016;14(1):68.

9. Otten MH, Anink J, Prince FH, Twilt M, Vastert SJ, ten Cate R, et al. Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch national Arthritis and Biologics in Children Register. Ann Rheum Dis. 2015;74(7):1379-1386.
10. Tarkiainen M, Tynjala P, Vahasalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatology (Oxford). 2015;54(7):1170-1176.
11. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol. 2014;66(9):2580-2589.
12. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, et al. Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. Rheumatology (Oxford). 2012;51(8):1407-1415.
13. Halbig M, Horneff G. Improvement of functional ability in children with juvenile idiopathic arthritis by treatment with etanercept. Rheumatol Int. 2009;30(2):229-238.
14. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009;68(5):635-641.

PICO 51. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS > 2.51) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. However, the studies[1-4] used to address PICO 46 (for patients without risk factors) did include a minority of patients (22%) who were RF+. For more information see the text summary and tables under PICO 46.

Quality of evidence across all critical outcomes: Very low

References

1. Ruperto N, Lovell DJ, Li T, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M, et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2010;62(11):1542-1551.

2. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383-391.

3. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(6):1792-1802.

4. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Perez N, Silva CA, et al. Long-term safety, efficacy and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arth Rheum 2015; 67(10):2759-2770.

PICO 52. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS > 2.51) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. However, the RCT[1] used to address PICO 47 (for patients without risk factors) did include a minority of patients (29%) who were RF+. For further information, see the text summary and tables under PICO 47.

Quality of evidence across all critical outcomes: Very low

References

1. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74(6):1110-1117.

PICO 53. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) plus risk factors, receiving TNFi (+/-non-biologic DMARD), should changing to second drug within same class (TNFi) versus changing to different drug in different OBRM class be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. However, the two observational cohort studies[1,2] used to address PICO 48 (for patients without risk factors) included a small fraction of patients (6-12%) who were RF+. For more information see the text summary and tables under PICO 48.

Quality of evidence across all critical outcomes: Very low

References

1. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.
2. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol. 2014;66(9):2580-2589.

PICO 54. In children and adolescents with JIA and polyarthritis with moderate/high disease activity (cJADAS> 2.51) plus risk factors, should rituximab versus 3rd class OBRM approved for JIA be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question where the majority of patients had risk factors. However, the observational cohort study[1] used to address PICO 49 (for patients without risk factors) included a very small fraction of patients (4.6%) who were RF+. For more information see the text summary and table under PICO 49.

Quality of evidence across all critical outcomes: Very low

References:

1. Tarkiainen M. et al., Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. 2014, Rheumatology 2015;54:11701176, doi:10.1093/rheumatology/keu457

PICO 55: In children and adolescents with JIA and polyarthritis regardless of disease activity and risk factors, should PT or no PT (regardless of concomitant medical therapy) be recommended?

Summary: This PICO was addressed indirectly by one RCT comparing PT to PT + EMG biofeedback[1] and one prospective observational study.[2] The RCT showed with statistical significance that at 12 weeks PT with EMG biofeedback reduced pain greater than PT alone, while at 6 weeks there was no difference (Table 1). The observational study showed that low impact exercise reduced pain in the study subjects (Table 2).

Quality of evidence across all critical outcomes: Low

Table 1. PT compared to PT + EMG for health problem or population [1]

Bibliography: Eid MA, Aly SM, El-Shamy SM. Effect of Electromyographic Biofeedback Training on Pain, Quadriceps Muscle Strength, and Functional Ability in Juvenile Rheumatoid Arthritis. Am J Phys Med Rehabil. 2016;95(12):921-930.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With PT	With PT + EMG		Risk with PT	Risk difference with PT + EMG
Reduction in Pain (VAS) at 6 weeks											
36 (1 RCT)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	18	18	**No difference**	-	MD **0** (0.02 lower to 0.02 higher)
Reduction in Pain (VAS) at 12 weeks											
36 (1 RCT)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	18	18	**Favors PT + EMG**	-	MD **1.61 higher** (1.56 higher to 1.66 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Allocation, blinding, and attrition not reported

b. Compares PT to PT + EMG biofeedback

Table 2. Uncontrolled Observational Study of Low-impact Exercise

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
630, Klepper S., 2001 [2]	Prospective observational study	8-week, 24-session program	25 children and adolescents, 2 boys and 23 girls, with chronic polyarticular JRA	low-impact exercise	Significant improvement was found in the ASI (Friedman analysis of variance [ANOVA]), JC, and 9-minute run–walk test (repeated measures ANOVA) from the pre- to post-exercise tests. Mean VAS pain scores decreased 16% from study entry to the post-exercise test. Statistically significant improvement (reliable change index > 1.96) occurred in 80% of subjects on the ASI and 72% on the JC.

References

1. Eid MA, Aly SM, El-Shamy SM. Effect of Electromyographic Biofeedback Training on Pain, Quadriceps Muscle Strength, and Functional Ability in Juvenile Rheumatoid Arthritis. Am J Phys Med Rehabil. 2016;95(12):921-930.
2. Klepper SE. Effects of an eight-week physical conditioning program on disease signs and symptoms in children with chronic arthritis. Arthritis Care Res. 1999;12(1):52-60.

PICO 56. In children and adolescents with JIA and polyarthritis regardless of disease activity and risk factors, should OT versus no OT (regardless of concomitant medical therapy) be recommended?

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

Quality of evidence across all critical outcomes: Very low

Sacroiliitis/Enthesitis

PICO 1. In children and adolescents with active sacroiliitis, should treatment with NSAID monotherapy versus no treatment with an NSAID in improving outcomes be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 2. In children and adolescents with active sacroiliitis, is treatment with an NSAID in addition to ongoing therapy with a systemic DMARD or TNFi more effective than no treatment with an NSAID in improving outcomes?

Summary: This PICO was indirectly addressed by two placebo-controlled RCTs in which patients were receiving concomitant NSAIDs.[1,2] Etanercept was favored over placebo for no JIA flares at 48 weeks. One SAE was reported in the etanercept group (Table 1).[1] Adalimumab was favored over placebo for ACR 70 and BASDAI 50 response at 12 weeks. One SAE was reported in the adalimumab group (Table 2).[2] One retrospective cohort study of 217 children with enthesitis-related arthritis used multivariate modeling to identify significant associations between specific treatments and outcomes. csDMARDs were associated with a significant reduction in tender entheses count compared to other drug classes (TNFi, NSAIDs, and systemic glucocorticoids). TNFi was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs, NSAIDs, and systemic glucocorticoids)(Table 3).[3]

Quality of evidence across all critical outcomes: Low

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With ETN		Risk with Pbo	Risk difference with ETN
Patients with no JIA Flare at 48wks											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/18 (50.0%)	17/20 (85.0%)	**OR 5.67** (1.22 to 26.33) **Favors ETN**	500 per 1,000	**350 more per 1,000** (50 more to 463 more)
SAEs											

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/18 (0.0%)	1/20 (5.0%)	**OR 2.85** (0.11 to 74.38)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, half of the patients in both groups received concomitant NSAIDs

c. Small single study

d. Small single study. Wide 95% CI that overlaps the line of no difference.

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Ada**		**Risk with Placebo**	**Risk difference with Ada**
Total enthesis count, mean change at week 12											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1.7 lower** (5.04 lower to 1.64 higher)
MASES (0-13), mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1 lower** (2.48 lower to 0.48 higher)
SPARCC enthesitis index (0-16), mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **0.2 lower** (1.99 lower to 1.59 higher)
SAEs											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	0/15 (0.0%)	1/31 (3.2%)	**OR 1.52** (0.06 to 39.65)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
ACR30 response											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/15 (60.0%)	22/31 (71.0%)	**OR 1.63** (0.45 to 5.93)	600 per 1,000	**110 more per 1,000** (197 fewer to 299 more)
ACR50 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/15 (40.0%)	21/31 (67.7%)	**OR 3.15** (0.88 to 11.31)	400 per 1,000	**277 more per 1,000** (30 fewer to 483 more)
ACR70 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	17/31 (54.8%)	**OR 4.86** (1.14 to 20.70) **Favors Ada**	200 per 1,000	**349 more per 1,000** (22 more to 638 more)
ACR90 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	13/31 (41.9%)	**OR 4.69** (0.90 to 24.46)	133 per 1,000	**286 more per 1,000** (12 fewer to 657 more)
Patient assessment of total back pain, mean change at 12 weeks											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **5.1 lower** (19.89 lower to 9.69 higher)
Parent's assessment of patient's pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **12.6 lower** (27.59 lower to 2.39 higher)
BASDAI 50 response, 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	4/15 (26.7%)	19/31 (61.3%)	**OR 4.35** (1.12 to 16.85) **Favors Ada**	267 per 1,000	**346 more per 1,000** (23 more to 593 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, the majority of patients in both groups received concomitant NSAIDs

c. Small single study with only 1 event.

d. Small single study. Wide 95% CI that overlaps the line of no difference.

e. Small single study

Table 3. TNFi and csDMARDS in Children with Enthesitis-related Arthritis

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[3]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.

References

1. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.
2. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.
3. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

PICO 3. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with sulfasalazine compared to no treatment with sulfasalazine be recommended?

Summary: One randomized placebo-controlled study addressed this PICO question.[1] The population (Juvenile SpA) was indirect and the study measured 13 outcomes including active joint count, tender enthesitis count, physician assessment improved/worsened, patient assessment improved/worsened, cervical pain, and lumbar pain. All outcomes are imprecise except patient assessment improved and morning stiffness, which showed a statistically significant difference favoring sulfasalazine over placebo for patient assessment improved and favoring placebo over sulfasalazine for morning stiffness. There were no severe adverse events or medication side effects that lead to discontinuation of treatment.

Quality of evidence across all critical outcomes: Low

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Lumbar pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	1/17 (5.9%)	**OR 0.27** (0.03 to 2.92)	188 per 1,000	**129 fewer per 1,000** (181 fewer to 215 more)
Cervical pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	0/17 (0.0%)	**OR 0.11** (0.01 to 2.32)	188 per 1,000	**163 fewer per 1,000** (185 fewer to 161 more)
Anterior spinal flexion (cm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.4 lower** (1.07 lower to 0.27 higher)

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Active joint count, absolute decrease in mean											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.5 lower** (2.7 lower to 1.7 higher)
Tender enthesitis count (mean decrease)											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **1.9 lower** (5.62 lower to 1.82 higher)
Physician assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	10/17 (58.8%)	**OR 4.29** (0.97 to 18.97)	250 per 1,000	**338 more per 1,000** (6 fewer to 613 more)
Physician assessment worsened											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/16 (12.5%)	4/17 (23.5%)	**OR 2.15** (0.34 to 13.80)	125 per 1,000	**110 more per 1,000** (79 fewer to 538 more)
Patients assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [c]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	11/17 (64.7%)	**OR 5.50** (1.22 to 24.81) **Favors SSZ**	250 per 1,000	**397 more per 1,000** (39 more to 642 more)

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Patients assessment worsened											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/16 (31.3%)	4/17 (23.5%)	**OR 0.68** (0.15 to 3.16)	313 per 1,000	**76 fewer per 1,000** (249 fewer to 277 more)
Pain VAS (0-100 mm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.3 higher** (14.06 lower to 18.66 higher)
Areas of foot swelling (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.9 lower** (4.33 lower to 2.53 higher)
Areas of foot tenderness (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.1 lower** (6.67 lower to 2.47 higher)
Morning stiffness (min), mean change at 26 weeks											
33 (1 RCT)	serious [d]	not serious	serious [a]	not serious	none	⨁⨁◯◯ LOW	16	17	-	-	MD **22.6 lower** (39.33 lower to 5.87 lower) Favors placebo

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Patients with Juvenile SpA

b. Wide CI crossing significant effect threshold and no-effect line

c. Single study with small number of patients and events

d. Large between-group difference in baseline values for morning stiffness

References

1. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis. 2002;61(10):941-942.

PICO 4. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with methotrexate versus no treatment with methotrexate be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. One retrospective cohort study of 217 children with enthesitis-related arthritis indirectly addressed the question using multivariate modeling to identify significant associations between specific treatments and outcomes. TNFi was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs [including MTX], NSAIDs, and systemic glucocorticoids). csDMARDs were associated with a significant reduction only for one outcome (lower tender entheses count)(Table 1).

Quality of evidence across all critical outcomes: Very low

Table 1. TNFi and csDMARDS in Children with Enthesitis-related Arthritis

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[1]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). Tender entheses count: csDMARDs were associated with significant reduction in tender entheses compared to other medications (estimate -0.26, p=0.02). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.

References

1. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

PICO 5. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with TNFi compared to no treatment with TNFi be recommended?

Summary: One randomized placebo-controlled study addressed this PICO question.[1] The population (Juvenile SpA) was indirect and the study measured twelve relevant outcomes including 12-week followup for ASAS40, SAE, PedACR30, PedACR70, mean CHAQ-DI score, mean ESR, mean CRP, mean BASDAI spinal inflammation, mean back pain score, and mean BASFAI score . All outcomes are imprecise except two outcomes (mean ESR and mean BASDAI spinal inflammation score), which showed a statistically significant difference favoring adalimumab over placebo. All outcomes favor use of adalimumab, except severe adverse events, but the results are imprecise. The observational study summarized in PICO 4 also provides indirect evidence,[2] but at a lower quality level than the RCT by Horneff et al.

Quality of evidence across all critical outcomes: Low

Adalimumab compared to Placebo for Sacroiliitis

Bibliography: Horneff, G., et al (2012). Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther, 14(5), R230. doi:10.1186/ar4072

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Adalimumab		Risk with Placebo	Risk difference with Adalimumab
ASAS40 at wk 4											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	7/17 (41.2%)	**OR 2.80** (0.57 to 13.75)	200 per 1,000	**212 more per 1,000** (75 fewer to 575 more)
ASAS40 at wk 8											

Adalimumab compared to Placebo for Sacroiliitis

Bibliography: Horneff, G., et al (2012). Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther, 14(5), R230. doi:10.1186/ar4072

Quality assessment							Summary of findings				
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	9/17 (52.9%)	**OR 4.50** (0.92 to 21.92)	200 per 1,000	**329 more per 1,000** (13 fewer to 646 more)
Mean BASDAI spinal inflammation at wk12											
32 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	15	17	-	-	MD **2.3 lower** (4.02 lower to 0.58 lower) **Favors ADA**
Mean back pain score at wk12											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	15	17	-	-	MD **1.5 lower** (3.34 lower to 0.34 higher)
Mean BASFI score at wk12											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	15	17	-	-	MD **1.3 lower** (3.01 lower to 0.41 higher)
ASAS40 at wk 12											

Adalimumab compared to Placebo for Sacroiliitis

Bibliography: Horneff, G., et al (2012). Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther, 14(5), R230. doi:10.1186/ar4072

Quality assessment							Summary of findings				
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	5/15 (33.3%)	9/17 (52.9%)	**OR 2.25** (0.54 to 9.45)	333 per 1,000	**196 more per 1,000** (121 fewer to 492 more)
SAE Double blind phase											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	1/15 (6.7%)	2/17 (11.8%)	**OR 1.87** (0.15 to 22.94)	67 per 1,000	**51 more per 1,000** (56 fewer to 554 more)
PedACR30 wk 12											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	6/15 (40.0%)	11/17 (64.7%)	**OR 2.75** (0.66 to 11.54)	400 per 1,000	**247 more per 1,000** (94 fewer to 485 more)
PedACR70 wk 12											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	4/15 (26.7%)	9/17 (52.9%)	**OR 3.09** (0.70 to 13.71)	267 per 1,000	**262 more per 1,000** (64 fewer to 566 more)
Mean CHAQ-DI score at wk12											

Adalimumab compared to Placebo for Sacroiliitis

Bibliography: Horneff, G., et al (2012). Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther, 14(5), R230. doi:10.1186/ar4072

Quality assessment							Summary of findings				
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	15	17	-	-	MD **0.2 lower** (0.65 lower to 0.25 higher)
Mean ESR at wk12											
32 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	15	17	-	-	MD **12 lower** (22.22 lower to 1.78 lower) Favors ADA
Mean CRP at wk12											
32 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	15	17	-	-	MD **6 lower** (19.16 lower to 7.16 higher)

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Indirect population - juvenile onset ankylosing spondylitis patients

b. Wide CI crossing significant effect and no-effect thresholds

References

1. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012;14(5):R230.

2. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

PICO 6. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with systemic corticosteroids versus no treatment with systemic corticosteroids be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 7. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with systemic corticosteroids versus sulfasalazine be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 8. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus no intraarticular glucocorticoids be recommended?

Summary. One retrospective study indirectly addressed this question in a pediatric population.{1] All patients in the study received intraarticular glucocorticoid injections; the comparison was pre-post, there was no comparison to a parallel group of patients without injections. Therapeutic success measured by reduction of inflammatory activity was achieved in 11/14 patients (79%) following one or two consecutive sacroiliac joint injections. See results in table 1 below.

Table 2 provides a summary of data taken from PICO 13 in the 2015 ACR/SAA/SPARTAN guideline Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. The studies in table 2 enrolled primarily adult patients with spondyloarthropathies, so they provide only indirect evidence for PICO 8. The evidence report states the following: "This PICO was directly addressed by two small RCTs of poor quality.[2,3] The RCTs used non-standardized outcomes and one was not blinded. The PICO was also addressed by 2 observational pre/post studies (n=34 total) with 18 month follow-up that consistently showed improvement of about 40 mm in a 0-100 mm pain scale lasting 9 months.[4,5] Three additional observational studies included 51 AS patients and 44 uSpA patients. Results (which were not reported separately for AS) were very similar to the results of the RCTs (references not provided)." As shown in Table 2, the quality of evidence was rated as Very low.

Quality of evidence across all critical outcomes: Very low

Table 1. Intraarticular Glucocorticoid Injections in Children with Refractory Enthesitis-related Arthritis

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4316, Fritz F.,2011	Retrospective analysis	24 months	14 children with with refractory enthesitis-related arthritis	MR imaging guided sacroiliac joint injections of 20 mg triamcinolone acetonide	Success of therapy was achieved in 11/14 (79%) children. 7/11 (64%) responders required two consecutive sacroiliac joint injections for the achievement of success of therapy. Sacroiliac inflammation decreased significantly (−59%). Median remission time was 13.7 months. In 3/14 subjects (21%), the reduction of sacroiliac inflammatory activity was unsatisfactory despite two consecutive sacroiliac joint injections (non-responder group). VAS scores changed significantly by −2(−2–5) (−50%) from 4(1–6) at baseline to 2(1–6) at 7 weeks follow-up after the final injection procedure (p=0.021). In the responder group, VAS score changed by −2(−2–5) (−50%) from 4(1–6) at baseline to 2(1–3) (p=0.005). In the non-responder group, VAS score changed from 5(1–6) at baseline to

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					4(1–6) (p=1.000). No erosions occurred.

Table 2. Intraarticular Glucocorticoid Injections in Adults with Spondyloarthropathies

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With no GC	With GC		Risk with no GC	Risk difference with GC
Health Status: Pain (follow-up mean 1.5 months; range of scores 0 – 100; Better indicated by lower values)											
24 (2 RCTs)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	13	11	-	-	MD **20 lower** (unable to calculate CI)
Health Status: Pain at 9 months (follow-up mean 18 months; range of scores: 0-100; Better indicated by lower values)											
85 (4 observational)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	-	85	-	-	mean 45 lower (unable to calculate CI)

GC: glucocorticoids

Explanations

a. small numbers; not blinded

b. Met ESSG + AMOR and specifies that patients have AS, but not clear that all patients met mNYCC. Individuals with SAPHO excluded.

c. Measure is non-standardized

References:

1. Fritz F. et al. Evaluation of MR imaging guided steroid injection of the sacroiliac joints for the treatment of children with refractory enthesitis-related arthritis, Eur Radiol (2011) 21:1050–1057. DOI 10.1007/s00330-010-1994-1
2. Maugars Y, Mathis C, Berthelot J-M, Charlier C, Prost A. Assessment of the efficacy of sacroiliac corticosteroid injections in spondyloarthropathies: A double-blind study. Br J Rheumatol 1996;35:767-70.
3. Luukkainen R, Nissila M, Asikainen E, Sanila M, Lehtinen K, Alanaatu A, et al. Periarticular corticosteroid treatment of the sacroiliac joint in patients with seronegative spondylarthropathy. Clin Exp Rheumatol 1999;17:88-90.
4. Gunaydin I, Pereira PL, Fritz J, Konig C, Kotter I. Magnetic resonance imaging guided corticosteroid injection of sacroiliac joints in patients with spondylarthropathy. Are multiple injections more beneficial? Rheumatol Int 2006;26:396-400.
5. Migliore A, Bizzi E, Massafra U, Vacca F, Martin-Martin LS, Granata M, et al. A new technical contribution for ultrasound-guided injections of sacro-iliac joints. Eur Rev Med Pharmacol Sci. 2010 May;14(5):465-9.

PICO 9. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus sulfasalazine be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 10. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus TNFi be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 11. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with TNFi versus sulfasalazine be recommended?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. One retrospective cohort study of 217 children with enthesitis-related arthritis indirectly addressed the question using multivariate modeling to identify significant associations between specific treatments and outcomes. TNFi was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs [including SFZ], NSAIDs, and systemic glucocorticoids). csDMARDs were associated with a significant reduction only for one outcome (lower tender entheses count)(Table 1).

Quality of evidence across all critical outcomes: Very low

Table 1. TNFi and csDMARDS in Children with Enthesitis-related Arthritis

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[1]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). Tender entheses count: csDMARDs were associated with significant reduction in tender entheses compared to other medications (estimate -0.26, p=0.02). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.

References

1. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

PICO 12. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with TNFi versus systemic corticosteroids be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 13. In children and adolescents with active enthesitis, should NSAID monotherapy versus no NSAIDs be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 14: In children and adolescents with active enthesitis, is treatment with an NSAID in addition to ongoing therapy with a systemic DMARD or biologic more effective than no treatment with an NSAID in improving outcomes?

Summary: This PICO was indirectly addressed by two placebo-controlled RCTs in which patients were receiving concomitant NSAIDs.[1,2] Etanercept was favored over placebo for no JIA flares at 48 weeks. One SAE was reported in the etanercept group (Table 1).[1] Adalimumab was favored over placebo for ACR 70 and BASDAI 50 response at 12 weeks. One SAE was reported in the adalimumab group (Table 2).[2]

One retrospective cohort study of 217 children with enthesitis-related arthritis used multivariate modeling to identify significant associations between specific treatments and outcomes. csDMARDs were associated with a significant reduction only for tender entheses count compared to other medications. TNFi was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs, NSAIDs, and systemic glucocorticoids)(Table 3).[3]

Quality of evidence across all critical outcomes: Low

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With ETN		Risk with Pbo	Risk difference with ETN
Patients with no JIA Flare at 48wks											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/18 (50.0%)	17/20 (85.0%)	**OR 5.67** (1.22 to 26.33) **Favors ETN**	500 per 1,000	**350 more per 1,000** (50 more to 463 more)
SAEs											

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/18 (0.0%)	1/20 (5.0%)	**OR 2.85** (0.11 to 74.38)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, half of the patients in both groups received concomitant NSAIDs

c. Small single study

d. Small single study. Wide 95% CI that overlaps the line of no difference.

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Ada**		**Risk with Placebo**	**Risk difference with Ada**
Total enthesis count, mean change at week 12											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1.7 lower** (5.04 lower to 1.64 higher)
MASES (0-13), mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1 lower** (2.48 lower to 0.48 higher)
SPARCC enthesitis index (0-16), mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **0.2 lower** (1.99 lower to 1.59 higher)
SAEs											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	0/15 (0.0%)	1/31 (3.2%)	**OR 1.52** (0.06 to 39.65)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
ACR30 response											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/15 (60.0%)	22/31 (71.0%)	**OR 1.63** (0.45 to 5.93)	600 per 1,000	**110 more per 1,000** (197 fewer to 299 more)
ACR50 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/15 (40.0%)	21/31 (67.7%)	**OR 3.15** (0.88 to 11.31)	400 per 1,000	**277 more per 1,000** (30 fewer to 483 more)
ACR70 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	17/31 (54.8%)	**OR 4.86** (1.14 to 20.70) **Favors Ada**	200 per 1,000	**349 more per 1,000** (22 more to 638 more)
ACR90 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	13/31 (41.9%)	**OR 4.69** (0.90 to 24.46)	133 per 1,000	**286 more per 1,000** (12 fewer to 657 more)
Patient assessment of total back pain, mean change at 12 weeks											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **5.1 lower** (19.89 lower to 9.69 higher)
Parent's assessment of patient's pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **12.6 lower** (27.59 lower to 2.39 higher)
BASDAI 50 response, 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	4/15 (26.7%)	19/31 (61.3%)	**OR 4.35** (1.12 to 16.85) **Favors Ada**	267 per 1,000	**346 more per 1,000** (23 more to 593 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, the majority of patients in both groups received concomitant NSAIDs

c. Small single study with only 1 event.

d. Small single study. Wide 95% CI that overlaps the line of no difference.

e. Small single study

Table 3. TNFi and csDMARDS in Children with Enthesitis-related Arthritis

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[3]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Tender entheses count: csDMARDs were associated with significant reduction in tender entheses compared to other medications (estimate -0.26, p=0.02). Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.

References

1. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.
2. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.
3. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

PICO 15: In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with methotrexate versus TNFi be recommended?

Summary: This PICO was indirectly addressed by two placebo-controlled RCTs in which patients were receiving concomitant NSAIDs,[1,2] one retrospective cohort study comparing different drug classes (including TNFi and csDMARDs)[3] and four single-arm observational studies evaluating etanercept administration to patients with enthesitis.[4-7]

Etanercept was favored over placebo for no JIA flares at 48 weeks. One SAE was reported in the etanercept group (Table 1).[1] Abatacept was favored over placebo for ACR 70 and BASDAI 50 response at 12 weeks. One SAE was reported in the adalimumab group (Table 2).[2]

One retrospective cohort study of 217 children with enthesitis-related arthritis used multivariate modeling to identify significant associations between specific treatments and outcomes. csDMARDs as a group were associated with a significant reduction only for tender entheses count compared to other medications. TNFi as a group was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs, NSAIDs, and systemic glucocorticoids)(Table 3).[3]

Evidence from the single-arm observational studies indicated that the ACR30 was achieved by 83% at 12 weeks,[4] and by 72% at 24 months in separate studies.[6] ACR50 was achieved by 81% at 12 weeks to 68% by 24 months,[4,5] and ACR70 61% at 12 weeks[4] to 57% at 24 months.[6] Active Joint decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4,[5] JADAS-10 decreased from 15.3 +/- 7.2 to 4.5. ESR, CRP, and CHAQ decreased by 56%, 67%, and 61% respectively. Duration of morning stiffness, number of tender joints, number of swollen joints, and number of joints with limitation of motion decreased by 71%, 69%, 81%, and 52%, respectively.[6] Serious adverse events ranged from 0.8% at 12 weeks up to 7% and 17.9 events/100 patient-years at 24 months in separate studies.[4,6,7] Lastly, at median 22 months followup, 61% of patients with ERA had an HAQ score of 0 (Table 3).[5]

Quality of evidence across all critical outcomes: Low

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With ETN		Risk with Placebo	Risk difference with ETN

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
Patients with no JIA Flare at 48wks											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/18 (50.0%)	17/20 (85.0%)	**OR 5.67** (1.22 to 26.33) **Favors ETN**	500 per 1,000	**350 more per 1,000** (50 more to 463 more)
SAEs											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/18 (0.0%)	1/20 (5.0%)	**OR 2.85** (0.11 to 74.38)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, half of the patients in both groups received concomitant NSAIDs

c. Small single study

d. Small single study. Wide 95% CI that overlaps the line of no difference.

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment	Summary of findings

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Pbo	With Ada		Risk with Pbo	Risk difference with Ada
SAEs											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	0/15 (0.0%)	1/31 (3.2%)	**OR 1.52** (0.06 to 39.65)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Total enthesis count, mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1.7 lower** (5.04 lower to 1.64 higher)
MASES (0-13), mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1 lower** (2.48 lower to 0.48 higher)
SPARCC enthesitis index (0-16), mean change at 12 weeks											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **0.2 lower** (1.99 lower to 1.59 higher)
ACR30 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/15 (60.0%)	22/31 (71.0%)	**OR 1.63** (0.45 to 5.93)	600 per 1,000	**110 more per 1,000** (197 fewer to 299 more)
ACR50 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/15 (40.0%)	21/31 (67.7%)	**OR 3.15** (0.88 to 11.31)	400 per 1,000	**277 more per 1,000** (30 fewer to 483 more)
ACR70 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	17/31 (54.8%)	**OR 4.86** (1.14 to 20.70) **Favors Ada**	200 per 1,000	**349 more per 1,000** (22 more to 638 more)
ACR90 response											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	13/31 (41.9%)	**OR 4.69** (0.90 to 24.46)	133 per 1,000	**286 more per 1,000** (12 fewer to 657 more)
Patient assessment of total back pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **5.1 lower** (19.89 lower to 9.69 higher)
Parent's assessment of patient's pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **12.6 lower** (27.59 lower to 2.39 higher)
BASDAI 50 response, 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	4/15 (26.7%)	19/31 (61.3%)	**OR 4.35** (1.12 to 16.85) **Favors Ada**	267 per 1,000	**346 more per 1,000** (23 more to 593 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, the majority of patients in both groups received concomitant NSAIDs

c. Small single study with only 1 event.

d. Small single study. Wide 95% CI that overlaps the line of no difference.

e. Small single study

Table 3: Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[3]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Tender entheses count: csDMARDs were associated with significant reduction in tender entheses compared to other medications (estimate -0.26, p=0.02). Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.
Horneff G., 2014[4]	Open-label retrospective cohort study (CLIPPER study)	12 weeks	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and	Etanercept (ETN) 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects	At 12 weeks JIA ACR 30 (95% CI) was achieved by 83.3% (67.2% to 93.6%) in patients with ERA. For ERA, the OR (95% CI) of ETN versus the historical placebo data was 15.1 (6.0 to 38.2). JIA ACR 50, 70 and 90 responses (95% CI) were achieved by 81.1% (73.1% to 87.7%), 61.5% (52.2% to 70.1%) and 29.8% (21.8% to 38.7%) of all patients, respectively.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			PsA n=29)	were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	In total, inactive disease (95% CI) was achieved by 11.9% (4.9% to 22.9%) by week 12 in subjects with ERA. Among all patients, two (1.6%) subjects withdrew from ETN treatment due to treatment-emergent serious infections. For non-infectious SAEs, there was one case (0.8%) of abdominal pain which led to hospitalization.
Constantin T., 2016 [7]	Open-label retrospective cohort study (CLIPPER study)	96 weeks (long-term follow-up of CLIPPER)	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and PsA n=29)	ETN 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	• Patients with ERA achieving JIA ACR 30/50/70/90/100 at Week 96 were 78.9% (62.7- 90.4), 76.3% (59.8- 88.6), 68.4% (51.3- 82.5), 52.6% • (35.8- 69.0), and 39.5% (24.0- 56.6), respectively. • PGA of disease activity changed from baseline mean of 5.4 (4.8, 6.0) to 0.6 (0.4, 0.9) with 87.1% improvement at week 96, • Patient/parent global assessment changed from baseline mean of 5.4 (4.7, 6.2) to 0.9 (0.5, 1.4) with 81.7% improvement at week 96, Number of active joints from 5.2 (4.0, 6.4) to 0.5 (0.2, 0.9) (88.5% improvement), • No. joints with LOM from 4.8 (3.5, 6.2) to 1.3 (0.3, 2.4) (71.7% improvement), • CRP, mg/l from 15.3 (8.2, 22.3) 2.7 (1.1, 4.3) (22.1% improvement) • CHAQ from 0.7 (0.6, 0.9) to 0.1 (0.0, 0.2) (82.4% improvement) • Parent global assessment of child's pain (VAS) from 5.8 (4.9, 6.6) to 0.9 (0.4, 1.3) (80.1% improvement) • Duration of morning stiffness in min from 89.3 (46.9, 131.7) to 10.7 (0.1, 21.2) (70.9% improvement) • JADAS from 17.2 (14.8, 19.6) to 2.2 (1.3, 3.0) (85.3% improvement) • There were 11 Serious AE among ERA patients (17.9 events per 100 patient-years)
Minden K 2012[5]	Prospective Observational Cohort Study (JUMBO registry)	Ongoing Started in 2007 and data for the current study was	346 Adult patients diagnosed with JIA in childhood AND who ever received ETN during childhood	ETN (no specific dose or duration of treatment required for entry). Outcomes are	At last follow-up (median 22 months for patients with ERA): For patients with ERA, 61% had an HAQ score of 0. AE/SAE (among all 346 patients) were rare: 2.1 severe infections and 1.5 new autoimmune events per 100 patient-years

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		collected through Dec 31 2010	AND who were assessed at least once in the JUMBO registry. 75 patients had ERA.	assessed every 6 months	
Windschall 2015[6]	Observational Study	24 months	238 patients Age 14.8 SD 2.8 (at baseline)	ETN Dose not mentioned	Active Joints decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4 JADAS-10 decreased from 15.3 +/- 7.2 to 4.5 Ped ACR30: 72% Ped ACR50: 68% Ped ACR70: 57% Patient and physician global assessment decreased by 65% ESR decreased by 56% CRP decreased by 67% CHAQ decreased by 61% Duration of morning stiffness decreased by 71% Number of tender joints decreased by 69% Number of swollen joints decreased by 81% Number of joints with limitation of motion decreased by 52% SAE: 17/238 (7%)

References:

1. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.
2. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.
3. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]

4. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2014;73(6):1114-1122.
5. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, et al. Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. Rheumatology (Oxford). 2012;51(8):1407-1415.
6. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol. 2015;34(1):61-69.
7. Constantin, T., Foeldvari, I., Vojinovic, J., Horneff, G., Burgos-Vargas, R., Nikishina, I., et al. (2016). Two-year Efficacy and Safety of Etanercept in Pediatric Patients with Extended Oligoarthritis, Enthesitis-related Arthritis, or Psoriatic Arthritis. J Rheumatol 2016; 43(4), 816-824.

PICO 16. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with methotrexate versus sulfasalazine be recommended?

Summary: One randomized placebo-controlled study addressed this PICO question.[1] The treatment comparison (sulfasalazine vs. placebo) was indirect and the study measured 13 outcomes including active joint count, tender enthesitis count, physician assessment improved/worsened, patient assessment improved/worsened, cervical pain, and lumbar pain. All outcomes are imprecise except patient assessment improved and morning stiffness, which showed a statistically significant difference favoring sulfasalazine over placebo for patient assessment improved and favoring placebo over sulfasalazine for morning stiffness. There were no severe adverse events or medication side effects that lead to discontinuation of treatment. No studies were identified using methotrexate in this population.

Quality of evidence across all critical outcomes: Low

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Tender enthesitis count (mean decrease)											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **1.9 lower** (5.62 lower to 1.82 higher)
Lumbar pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	1/17 (5.9%)	**OR 0.27** (0.03 to 2.92)	188 per 1,000	**129 fewer per 1,000** (181 fewer to 215 more)
Cervical pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	0/17 (0.0%)	**OR 0.11** (0.01 to 2.32)	188 per 1,000	**163 fewer per 1,000** (185 fewer to 161 more)

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Anterior spinal flexion (cm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.4 lower** (1.07 lower to 0.27 higher)
Active joint count, absolute decrease in mean											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.5 lower** (2.7 lower to 1.7 higher)
Physician assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	10/17 (58.8%)	**OR 4.29** (0.97 to 18.97)	250 per 1,000	**338 more per 1,000** (6 fewer to 613 more)
Physician assessment worsened											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/16 (12.5%)	4/17 (23.5%)	**OR 2.15** (0.34 to 13.80)	125 per 1,000	**110 more per 1,000** (79 fewer to 538 more)
Patients assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [c]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	11/17 (64.7%)	**OR 5.50** (1.22 to 24.81) **Favors SSZ**	250 per 1,000	**397 more per 1,000** (39 more to 642 more)
Patients assessment worsened											

SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/16 (31.3%)	4/17 (23.5%)	**OR 0.68** (0.15 to 3.16)	313 per 1,000	**76 fewer per 1,000** (249 fewer to 277 more)
Pain VAS (0-100 mm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.3 higher** (14.06 lower to 18.66 higher)
Areas of foot swelling (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.9 lower** (4.33 lower to 2.53 higher)
Areas of foot tenderness (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.1 lower** (6.67 lower to 2.47 higher)
Morning stiffness (min), mean change at 26 weeks											
33 (1 RCT)	serious [d]	not serious	serious [a]	not serious	none	⨁⨁◯◯ LOW	16	17	-	-	MD **22.6 lower** (39.33 lower to 5.87 lower) Favors placebo

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Compared sulfasalazine to placebo

b. Wide CI crossing significant effect threshold and no-effect line

c. Single study with small number of patients and events

d. Large between-group difference in baseline values for morning stiffness

References

1. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis. 2002;61(10):941-942.

PICO 17: In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with sulfasalazine versus TNFi be recommended?

Summary: This PICO was indirectly addressed by two placebo-controlled RCTs in which patients were receiving concomitant NSAIDs,[1,2] one retrospective cohort study comparing different drug classes (including TNFi and csDMARDs)[3] and four single-arm observational studies evaluating etanercept administration to patients with enthesitis.[4-7] An additional RCT compared sulfasalazine to placebo.[8]

Etanercept was favored over placebo for no JIA flares at 48 weeks. One SAE was reported in the etanercept group (Table 1).[1] Adalimumab was favored over placebo for ACR 70 and BASDAI 50 response at 12 weeks. One SAE was reported in the adalimumab group (Table 2).[2] For sulfasalazine, all outcomes were imprecise except patient assessment improved and morning stiffness, which showed a statistically significant difference favoring sulfasalazine over placebo for patient assessment improved and favoring placebo over sulfasalazine for morning stiffness (Table 3). There were no severe adverse events or medication side effects that lead to discontinuation of treatment in this trial.[8]

One retrospective cohort study of 217 children with enthesitis-related arthritis used multivariate modeling to identify significant associations between specific treatments and outcomes. csDMARDs as a group were associated with a significant reduction only for tender entheses count compared to other medications. TNFi as a group was associated with significant reductions in active joint count, cJADAS10 scores and patient-reported pain compared to other drug classes (csDMARDs, NSAIDs, and systemic glucocorticoids)(Table 4).[3]

Evidence from the single-arm observational studies indicated that the ACR30 was achieved by 83% at 12 weeks,[4] and by 72% at 24 months in separate studies.[6] ACR50 was achieved by 81% at 12 weeks to 68% by 24 months,[4,5] and ACR70 61% at 12 weeks[4] to 57% at 24 months.[6] Active Joint decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4,[5] JADAS-10 decreased from 15.3 +/- 7.2 to 4.5. ESR, CRP, and CHAQ decreased by 56%, 67%, and 61% respectively. Duration of morning stiffness, number of tender joints, number of swollen joints, and number of joints with limitation of motion decreased by 71%, 69%, 81%, and 52%, respectively.[6] Serious adverse events ranged from 0.8% at 12 weeks up to 7% and 17.9 events/100 patient-years at 24 months in separate studies.[4,6,7] Lastly, at median 22 months followup, 61% of patients with ERA had an HAQ score of 0 (Table 4).[5]

Quality of evidence across all critical outcomes: Low

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality	Study event rates (%)	Relative effect	Anticipated absolute effects

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
(studies) Follow-up	**bias**					**of evidence**	**With Placebo**	**With ETN**	**(95% CI)**	**Risk with Pbo**	**Risk difference with ETN**
Patients with no JIA Flare at 48wks											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/18 (50.0%)	17/20 (85.0%)	**OR 5.67** (1.22 to 26.33) **Favors ETN**	500 per 1,000	**350 more per 1,000** (50 more to 463 more)
SAEs											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/18 (0.0%)	1/20 (5.0%)	**OR 2.85** (0.11 to 74.38)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, half of the patients in both groups received concomitant NSAIDs

c. Small single study

d. Small single study. Wide 95% CI that overlaps the line of no difference.

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Pbo	With Ada		Risk with Pbo	Risk difference with Ada
SAEs											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	0/15 (0.0%)	1/31 (3.2%)	**OR 1.52** (0.06 to 39.65)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Total enthesis count, mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1.7 lower** (5.04 lower to 1.64 higher)
MASES (0-13), mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1 lower** (2.48 lower to 0.48 higher)
SPARCC enthesitis index (0-16), mean change at 12 weeks											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **0.2 lower** (1.99 lower to 1.59 higher)
ACR30 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/15 (60.0%)	22/31 (71.0%)	**OR 1.63** (0.45 to 5.93)	600 per 1,000	**110 more per 1,000** (197 fewer to 299 more)
ACR50 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/15 (40.0%)	21/31 (67.7%)	**OR 3.15** (0.88 to 11.31)	400 per 1,000	**277 more per 1,000** (30 fewer to 483 more)
ACR70 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	17/31 (54.8%)	**OR 4.86** (1.14 to 20.70) **Favors Ada**	200 per 1,000	**349 more per 1,000** (22 more to 638 more)
ACR90 response											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	13/31 (41.9%)	**OR 4.69** (0.90 to 24.46)	133 per 1,000	**286 more per 1,000** (12 fewer to 657 more)
Patient assessment of total back pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **5.1 lower** (19.89 lower to 9.69 higher)
Parent's assessment of patient's pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **12.6 lower** (27.59 lower to 2.39 higher)
BASDAI 50 response, 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	4/15 (26.7%)	19/31 (61.3%)	**OR 4.35** (1.12 to 16.85) **Favors Ada**	267 per 1,000	**346 more per 1,000** (23 more to 593 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, the majority of patients in both groups received concomitant NSAIDs

c. Small single study with only 1 event.

d. Small single study. Wide 95% CI that overlaps the line of no difference.

e. Small single study

Table 3. SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With SSZ**		**Risk with Placebo**	**Risk difference with SSZ**
Tender enthesitis count (mean decrease)											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **1.9 lower** (5.62 lower to 1.82 higher)
Lumbar pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	1/17 (5.9%)	**OR 0.27** (0.03 to 2.92)	188 per 1,000	**129 fewer per 1,000** (181 fewer to 215 more)
Cervical pain, 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/16 (18.8%)	0/17 (0.0%)	**OR 0.11** (0.01 to 2.32)	188 per 1,000	**163 fewer per 1,000** (185 fewer to 161 more)

Table 3. SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
Anterior spinal flexion (cm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.4 lower** (1.07 lower to 0.27 higher)
Active joint count, absolute decrease in mean											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.5 lower** (2.7 lower to 1.7 higher)
Physician assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	10/17 (58.8%)	**OR 4.29** (0.97 to 18.97)	250 per 1,000	**338 more per 1,000** (6 fewer to 613 more)
Physician assessment worsened											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/16 (12.5%)	4/17 (23.5%)	**OR 2.15** (0.34 to 13.80)	125 per 1,000	**110 more per 1,000** (79 fewer to 538 more)
Patients assessment improved											
33 (1 RCT)	not serious	not serious	serious [a]	serious [c]	none	⨁⨁◯◯ LOW	4/16 (25.0%)	11/17 (64.7%)	**OR 5.50** (1.22 to 24.81) **Favors SSZ**	250 per 1,000	**397 more per 1,000** (39 more to 642 more)
Patients assessment worsened											

Table 3. SSZ compared to Placebo for Enthesitis related JIA

Bibliography: Burgos-Vargas R. et al. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies, Ann Rheum Dis 2002;61:941–942

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With SSZ		Risk with Placebo	Risk difference with SSZ
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/16 (31.3%)	4/17 (23.5%)	**OR 0.68** (0.15 to 3.16)	313 per 1,000	**76 fewer per 1,000** (249 fewer to 277 more)
Pain VAS (0-100 mm), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.3 higher** (14.06 lower to 18.66 higher)
Areas of foot swelling (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **0.9 lower** (4.33 lower to 2.53 higher)
Areas of foot tenderness (count), mean change at 26 weeks											
33 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	16	17	-	-	MD **2.1 lower** (6.67 lower to 2.47 higher)
Morning stiffness (min), mean change at 26 weeks											
33 (1 RCT)	serious [d]	not serious	serious [a]	not serious	none	⨁⨁◯◯ LOW	16	17	-	-	MD **22.6 lower** (39.33 lower to 5.87 lower) Favors placebo

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Compared sulfasalazine to placebo

b. Wide CI crossing significant effect threshold and no-effect line

c. Single study with small number of patients and events

d. Large between-group difference in baseline values for morning stiffness

Table 4: Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7194, Weiss 2017[3]	Multicenter retrospective cohort study	1 year	217 Children with enthesitis-related arthritis; only 23% had sacroiliac joint tenderness and/or inflammatory spinal pain at baseline.	TNFi monotherapy (ETN, ADA, or IFX), csDMARD monotherapy (MTX, SSZ, or LFN), csDMARD + TNFi, NSAIDs and systemic glucocorticoids	Results of multivariate modeling: Tender entheses count: csDMARDs were associated with significant reduction in tender entheses compared to other medications (estimate -0.26, p=0.02). Active joint count: TNFi was associated with significant reduction in active joint count compared to other medications (estimate -0.78, p=0.03). cJADAS10: TNFi was associated with significant improvement in cJADAS10 scores compared to other medications (estimate -2.90, p<0.01). Patient reported pain (0-10): TNFi was associated with significant reduction in pain compared to other medications (estimate -1.23, p<0.01). JSpADA scores and patient-reported disease activity did not differ significantly between drug classes.
Horneff G., 2013[4]	Open-label study	12 weeks	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and PsA n=29)	Etanercept (ETN) 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	At 12 weeks JIA ACR 30 (95% CI) was achieved by 83.3% (67.2% to 93.6%) in patients with ERA. For ERA, the OR (95% CI) of ETN versus the historical placebo data was 15.1 (6.0 to 38.2). JIA ACR 50, 70 and 90 responses (95% CI) were achieved by 81.1% (73.1% to 87.7%), 61.5% (52.2% to 70.1%) and 29.8% (21.8% to 38.7%) of all patients, respectively. In total, inactive disease (95% CI) was achieved by 11.9% (4.9% to 22.9%) by week 12 in subjects with ERA. Among all patients, two (1.6%) subjects withdrew from ETN treatment due to treatment-emergent serious infections. For non-infectious SAEs, there was one case (0.8%) of abdominal pain which led to hospitalization.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Constantin T., 2016 [7]	Open-label retrospective cohort study (CLIPPER study)	96 weeks (long-term follow-up of CLIPPER)	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and PsA n=29)	ETN 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	• Patients with ERA achieving JIA ACR 30/50/70/90/100 at Week 96 were 78.9% (62.7- 90.4), 76.3% (59.8- 88.6), 68.4% (51.3- 82.5), 52.6% • (35.8- 69.0), and 39.5% (24.0- 56.6), respectively. • PGA of disease activity changed from baseline mean of 5.4 (4.8, 6.0) to 0.6 (0.4, 0.9) with 87.1% improvement at week 96, • Patient/parent global assessment changed from baseline mean of 5.4 (4.7, 6.2) to 0.9 (0.5, 1.4) with 81.7% improvement at week 96, Number of active joints from 5.2 (4.0, 6.4) to 0.5 (0.2, 0.9) (88.5% improvement), • No. joints with LOM from 4.8 (3.5, 6.2) to 1.3 (0.3, 2.4) (71.7% improvement), • CRP, mg/l from 15.3 (8.2, 22.3) 2.7 (1.1, 4.3) (22.1% improvement) • CHAQ from 0.7 (0.6, 0.9) to 0.1 (0.0, 0.2) (82.4% improvement) • Parent global assessment of child's pain (VAS) from 5.8 (4.9, 6.6) to 0.9 (0.4, 1.3) (80.1% improvement) • Duration of morning stiffness in min from 89.3 (46.9, 131.7) to 10.7 (0.1, 21.2) (70.9% improvement) • JADAS from 17.2 (14.8, 19.6) to 2.2 (1.3, 3.0) (85.3% improvement) There were 11 Serious AE among ERA patients (17.9 events per 100 patient-years)
Minden K 2012[5]	Prospective Observational Cohort Study (JUMBO registry)	Ongoing Started in 2007 and data for the current study was collected through Dec 31 2010	346 Adult patients diagnosed with JIA in childhood AND who ever received ETN during childhood AND who were assessed at least once in the JUMBO registry. 75 patients had ERA.	ETN (no specific dose or duration of treatment required for entry). Outcomes are assessed every 6 months	At last follow-up (median 22 months for patients with ERA): For patients with ERA, 61% had an HAQ score of 0. AE/SAE (among all 346 patients) were rare: 2.1 severe infections and 1.5 new autoimmune events per 100 patient-years
Windschall 2015[6]	Observational Study	24 months	238 patients Age 14.8 SD 2.8 (at baseline)	ETN Dose not mentioned	Active Joints decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4 JADAS-10 decreased from 15.3 +/- 7.2 to 4.5 Ped ACR30: 72% Ped ACR50: 68%

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Ped ACR70: 57% Patient and physician global assessment decreased by 65% ESR decreased by 56% CRP decreased by 67% CHAQ decreased by 61% Duration of morning stiffness decreased by 71% Number of tender joints decreased by 69% Number of swollen joints decreased by 81% Number of joints with limitation of motion decreased by 52% SAE: 17/238 (7%)

References:

1. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.
2. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.
3. Weiss PF, Xiao R, Brandon TG, Pagnini I, Wright TB, Beukelman T, et al. Comparative effectiveness of tumor necrosis factor agents and disease-modifying antirheumatic therapy in children with enthesitis-related arthritis: the first year after diagnosis. J Rheumatol 2017;44 (11); doi:10.3899/jrheum.170251. [Epub ahead of print]
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6. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol. 2015;34(1):61-69.
7. Constantin, T., Foeldvari, I., Vojinovic, J., Horneff, G., Burgos-Vargas, R., Nikishina, I., et al. (2016). Two-year Efficacy and Safety of Etanercept in Pediatric Patients with Extended Oligoarthritis, Enthesitis-related Arthritis, or Psoriatic Arthritis. J Rheumatol 2016; 43(4), 816-824.

8. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis. 2002;61(10):941-942.

PICO 18. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with systemic glucocorticoids versus TNFi be recommended?

Summary: This PICO was indirectly addressed by two placebo-controlled RCTs in which patients were receiving concomitant NSAIDs,[1,2] and four single-arm observational studies evaluating etanercept administration to patients with enthesitis.[3-6] Literature searches identified no studies that addressed this PICO in patients administered systemic glucocorticoids.

Etanercept was favored over placebo for no JIA flares at 48 weeks. One SAE was reported in the etanercept group (Table 1).[1] Abatacept was favored over placebo for ACR 70 and BASDAI 50 response at 12 weeks. One SAE was reported in the adalimumab group (Table 2).[2]

Evidence from the single-arm observational studies indicated that the ACR30 was achieved by 83% at 12 weeks,[3] and by 72% at 24 months in separate studies.[5] ACR50 was achieved by 81% at 12 weeks to 68% by 24 months,[3,5] and ACR70 61% at 12 weeks[3] to 57% at 24 months.[5] Active Joint decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4,[5] JADAS-10 decreased from 15.3 +/- 7.2 to 4.5. ESR, CRP, and CHAQ decreased by 56%, 67%, and 61% respectively. Duration of morning stiffness, number of tender joints, number of swollen joints, and number of joints with limitation of motion decreased by 71%, 69%, 81%, and 52%, respectively.[5] Serious adverse events ranged from 0.8% at 12 weeks up to 7% and 17.9 events/100 patient-years at 24 months in separate studies.[3,5,6] Lastly, at median 22 months followup, 61% of patients with ERA had an HAQ score of 0 (Table 3).[4]

Quality of evidence across all critical outcomes: Low

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With ETN		Risk with Placebo	Risk difference with ETN
Patients with no JIA Flare at 48wks											

Table 1. Etanercept vs. placebo for enthesitis-related arthritis

Bibliography: Horneff G, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.

Quality assessment							Summary of findings				
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	9/18 (50.0%)	17/20 (85.0%)	**OR 5.67** (1.22 to 26.33) **Favors ETN**	500 per 1,000	**350 more per 1,000** (50 more to 463 more)
SAEs											
38 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/18 (0.0%)	1/20 (5.0%)	**OR 2.85** (0.11 to 74.38)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, half of the patients in both groups received concomitant NSAIDs

c. Small single study

d. Small single study. Wide 95% CI that overlaps the line of no difference.

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings		
№ of participants	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality**	**Study event rates (%)**	**Relative effect**	**Anticipated absolute effects**

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
(studies) Follow-up	**bias**					**of evidence**	**With Pbo**	**With Ada**	**(95% CI)**	**Risk with Pbo**	**Risk difference with Ada**
SAEs											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	0/15 (0.0%)	1/31 (3.2%)	**OR 1.52** (0.06 to 39.65)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Total enthesis count, mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1.7 lower** (5.04 lower to 1.64 higher)
MASES (0-13), mean change at week 12											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **1 lower** (2.48 lower to 0.48 higher)
SPARCC enthesitis index (0-16), mean change at 12 weeks											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **0.2 lower** (1.99 lower to 1.59 higher)
ACR30 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	9/15 (60.0%)	22/31 (71.0%)	**OR 1.63** (0.45 to 5.93)	600 per 1,000	**110 more per 1,000** (197 fewer to 299 more)
ACR50 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/15 (40.0%)	21/31 (67.7%)	**OR 3.15** (0.88 to 11.31)	400 per 1,000	**277 more per 1,000** (30 fewer to 483 more)
ACR70 response											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	3/15 (20.0%)	17/31 (54.8%)	**OR 4.86** (1.14 to 20.70) **Favors Ada**	200 per 1,000	**349 more per 1,000** (22 more to 638 more)
ACR90 response											

Table 2. Adalimumab compared to placebo for enthesitis-related arthritis

Bibliography: Burgos-Vargas R, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

Quality assessment							Summary of findings				
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	13/31 (41.9%)	**OR 4.69** (0.90 to 24.46)	133 per 1,000	**286 more per 1,000** (12 fewer to 657 more)
Patient assessment of total back pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **5.1 lower** (19.89 lower to 9.69 higher)
Parent's assessment of patient's pain, mean change at 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	15	31	-	-	MD **12.6 lower** (27.59 lower to 2.39 higher)
BASDAI 50 response, 12 weeks											
46 (1 RCT)	not serious	not serious [a]	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	4/15 (26.7%)	19/31 (61.3%)	**OR 4.35** (1.12 to 16.85) **Favors Ada**	267 per 1,000	**346 more per 1,000** (23 more to 593 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not applicable

b. Indirect comparison, the majority of patients in both groups received concomitant NSAIDs

c. Small single study with only 1 event.

d. Small single study. Wide 95% CI that overlaps the line of no difference.

e. Small single study

Table 3: Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Horneff G., 2013[3]	Open-label study	12 weeks	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and PsA n=29)	Etanercept (ETN) 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	At 12 weeks JIA ACR 30 (95% CI) was achieved by 83.3% (67.2% to 93.6%) in patients with ERA. For ERA, the OR (95% CI) of ETN versus the historical placebo data was 15.1 (6.0 to 38.2). JIA ACR 50, 70 and 90 responses (95% CI) were achieved by 81.1% (73.1% to 87.7%), 61.5% (52.2% to 70.1%) and 29.8% (21.8% to 38.7%) of all patients, respectively. In total, inactive disease (95% CI) was achieved by 11.9% (4.9% to 22.9%) by week 12 in subjects with ERA. Among all patients, two (1.6%) subjects withdrew from ETN treatment due to treatment-emergent serious infections. For non-infectious SAEs, there was one case (0.8%) of abdominal pain which led to hospitalization.
Constantin T., 2016 [6]	Open-label retrospective cohort study (CLIPPER study)	96 weeks (long-term follow-up of CLIPPER)	127 subjects (extended oligoarticular JIA n=60, enthesitis-related arthritis (ERA) n=38 and PsA n=29)	ETN 0.8 mg/kg once weekly (maximum 50 mg). All 127 subjects were ≥80% compliant with ETN and 115 (90.6%) were 100% compliant.	• Patients with ERA achieving JIA ACR 30/50/70/90/100 at Week 96 were 78.9% (62.7- 90.4), 76.3% (59.8- 88.6), 68.4% (51.3- 82.5), 52.6% • (35.8- 69.0), and 39.5% (24.0- 56.6), respectively. • PGA of disease activity changed from baseline mean of 5.4 (4.8, 6.0) to 0.6 (0.4, 0.9) with 87.1% improvement at week 96, • Patient/parent global assessment changed from baseline mean of 5.4 (4.7, 6.2) to 0.9 (0.5, 1.4) with 81.7% improvement at week 96, Number of active joints from 5.2 (4.0, 6.4) to 0.5 (0.2, 0.9) (88.5% improvement), • No. joints with LOM from 4.8 (3.5, 6.2) to 1.3 (0.3, 2.4) (71.7% improvement), • CRP, mg/l from 15.3 (8.2, 22.3) 2.7 (1.1, 4.3) (22.1% improvement) • CHAQ from 0.7 (0.6, 0.9) to 0.1 (0.0, 0.2) (82.4% improvement) • Parent global assessment of child's pain (VAS) from 5.8 (4.9, 6.6) to 0.9 (0.4, 1.3)

					(80.1% improvement) • Duration of morning stiffness in min from 89.3 (46.9, 131.7) to 10.7 (0.1, 21.2) (70.9% improvement) • JADAS from 17.2 (14.8, 19.6) to 2.2 (1.3, 3.0) (85.3% improvement) There were 11 Serious AE among ERA patients (17.9 events per 100 patient-years)
Minden K 2012[4]	Prospective Observational Cohort Study (JUMBO registry)	Ongoing Started in 2007 and data for the current study was collected through Dec 31 2010	346 Adult patients diagnosed with JIA in childhood AND who ever received ETN during childhood AND who were assessed at least once in the JUMBO registry. 75 patients had ERA.	ETN (no specific dose or duration of treatment required for entry). Outcomes are assessed every 6 months	At last follow-up (median 22 months for patients with ERA): For patients with ERA, 61% had an HAQ score of 0. AE/SAE (among all 346 patients) were rare: 2.1 severe infections and 1.5 new autoimmune events per 100 patient-years
Windschall 2015[5]	Observational Study	24 months	238 patients Age 14.8 SD 2.8 (at baseline)	ETN Dose not mentioned	Active Joints decreased from 4.3 +/- 5.7 to 1.0 +/- 2.4 JADAS-10 decreased from 15.3 +/- 7.2 to 4.5 Ped ACR30: 72% Ped ACR50: 68% Ped ACR70: 57% Patient and physician global assessment decreased by 65% ESR decreased by 56% CRP decreased by 67% CHAQ decreased by 61% Duration of morning stiffness decreased by 71% Number of tender joints decreased by 69% Number of swollen joints decreased by 81% Number of joints with limitation of motion decreased by 52% SAE: 17/238 (7%)

References:

1. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015;67(8):2240-2249.
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5. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol. 2015;34(1):61-69.
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PICO 19. In children and adolescents with active sacroiliitis, should treatment with any form of PT versus no PT (regardless of concomitant medical therapy) be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 20. In children and adolescents with active enthesitis, should any form of PT versus no PT (regardless of concomitant medical therapy) be recommended?

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

Quality of evidence across all critical outcomes: Very low

Uveitis

PICO 1. In children and adolescents with JIA with high risk of developing uveitis (oligoarthritis or rheumatoid factor seronegative polyarticular JIA, psoriatic JIA, ANA+), does screening more frequently than current guidelines decrease risk of developing ocular complications of uveitis?

Summary. The literature searches did not identify any studies that directly addressed this PICO question. There were 6 cohort studies[1-6] and one case control study[7] that evaluated factors associated with uveitis onset such as ANA positivity and oligo-articular disease course. Two studies[2,7] found that more severe uveitis was associated with a shorter time to onset from diagnosis of arthritis compared to mild uveitis. One study[7] found that severe cases of uveitis more often occurred in males than females. All studies found that ocular complications are not infrequent in patients with uveitis under the current guidelines. One study[3], compared the AAP screening guidelines to Southwood guidelines and found that the Southwood guidelines identified a few uveitis patients earlier than the AAP guidelines. However, conversely, the AAP guidelines captured a few late onset cases that would have been missed by the Southwood guidelines. Results ultimately support screening for uveitis at least as often as current guidelines and reiterates that ANA positivity and oligoarticular disease are risk factors for uveitis. Results also raise concern that males suspected of being at risk for uveitis be followed more closely given the potential for more severe disease. However, the results do not address what screening interval is associated with the least ocular complications.

Overall quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
Papadopoulou 2017[1]	Retrospective Comparative Cohort (uveitis vs. no uveitis)	2002-2011	299 Patients with JIA (130 persistent oligo, 42 extended oligo, 63 RF-poly, 10 RF+ poly, 12 systemic, 17 enthesitis-related, 20 psoriatic, 5 unclassified)	All patients screened within 2-4 weeks of referral All patients screened until 12 years of age ANA+ OA onset <4 years old, screening every 3 months for 5 years and thereafter every 6 months All other JIA subtypes (except systemic JIA) if under 7 yo at onset, screening every 3 months for 2 years and	Ocular complications developed in 15 (46.8%) of the 32 children with uveitis. Severe uveitis developed in 13 children (5 with persistent OA, 4 with extended OA and 4 with RF-negative PolyA).

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
				thereafter every 6 months Oligoarthritis, ANA+ poly, psoriatic onset btw 7-12yo, screening every 6 months Systemic, ERA, ANA neg poly if onset 7-12, screening every 6 months for one year, then every 6 months Adolescents 12-16 with JIA regardless of subtype, screen once	
Zannin 2012[2]	Prospective Cohort	At least 1 year	60 Patients (54 persistent oligo, 6 extended oligo)	Intervals between consecutive ophthalmologic evaluations varied between 2 weeks and 2 months, depending on the uveitis course.	Mean time interval between arthritis to uveitis 21.6 +/- 36.5 months. Interval was shorter for patients with severe uveitis (11.8 months) vs. mild uveitis (25.8 months). By 24 months since the arthritis onset, 71.7% of patients developed uveitis 22/60 patients had ocular complications: in 10 they were already present at disease onset and 12 developed them during the F/U 80% of those with severe ocular inflammation presented the first episode of uveitis by 5 months since the arthritis onset.
Reininga 2008[3]	Retrospective analysis	1 year	153 patients (14 systemic, 76 oligo, 48 RF-poly, 6 RF+ poly, 2 psoriatic, 5 enthesitis-	The authors propose combining frequency of Southwood and duration of AAP screening guidelines. The Southwood guidelines state “If [chronic iridocyclitis]CI is not detected initially [by slit	27 patients developed asymptomatic anterior uveitis 8 Dx at initial ophthalmologic screening 16 Dx at avg 43 months after arthritis onset (median 32 months, range 10-132 months) **AAP Uveitis risk category** High: 11/31 developed uveitis Moderate: 12/48 developed uveitis

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
			related, 2 other)	lamp screening after arthritis diagnosis], all children with JCA should be screened by slit lamp examinations every 3-4 months for the first 5 years after arthritis onset. After 5 years, CI screening could be stopped. The only exceptions would be arthritic children at low risk for CI, including systemic onset JCA, juvenile spondyloarthropathy and juvenile onset rheumatoid arthritis, who do not need to be screened if the initial slit lamp examination is normal."	Low: 4/74 developed uveitis 13.1% of patients classified as moderate or low risk developed uveitis. Ocular complications occurred in 13/27 patients (48.1%). By applying the AAP screening guidelines there would be a possible delay of 3 (moderate risk) - 9 months (low risk) before uveitis detection. These would have been detected by Southwood guidelines which screen more frequently AAP screens indefinitely and 3 patients who developed uveitis would have been missed by the Southwood guidelines (71, 92, and 133 months after arthritis) By applying Southwood's screening frequency, children with RF+, systemic onset and enthesitis associated uveitis are the ones at risk of late detection; 1 in 16 children in our population. By applying the AAP guidelines, children in the high risk categories would be screened at equal frequencies as under the Southwood guidelines (quarterly, n = 7/16), and 9 of 16 children would have been classified as intermediate or low risk and would have been screened at lower frequencies (every 6 months in the moderate and annually in the low risk categories.
Helilgenhaus 2007[4]	Cohort study	1 year	3271 patients (1497 persistent oligo, 227 extended oligo, 405 RF- poly, 67 RF+ poly, 198 systemic, 384	Screening interval not reported, but based on the study results the authors recommend differing screening intervals (ranging from 3 to 12 months) based on JIA subgroup, ANA status, age at JIA onset, and JIA duration. (see Table 6 in original publication for full details).	406 (12%) patients developed uveitis. 115 of the uveitis patients had ophthalmologic data. Median onset of uveitis was 5.5 months after arthritis. Mean onset of uveitis was 21 months after arthritis. Uveitis appearance occurred simultaneously with or within 6 months of arthritis onset in 48%, within the first 12 months of arthritis onset in 73% 59/106 (56%) patients had uveitis complications by the final visit (mean 5.6 years, SD 4.9 years). In univariate logistic regression, presence of complication

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
			enthesitis-related, 251 psoriatic, 242 other)		at first visit (P<0.001, OR 80.2, CI 16.7–383.9) and manifestation of uveitis before arthritis (P<0.001, OR 20.8, CI 2.5–171.4) were the only significant predictors of uveitis complications at the final visit.
Grassi 2007[5]	Retrospective cohort	Follow up: 7.6 +/- 5.6 years	309 patients (193 oligo, 66 poly, 50 systemic) Age at JIA onset: 4.9 y/o +/- 3.6 years	All patients had slit-lamp examinations every 3 to 6 months to assess the presence of uveitis and complications.	62/309 (20.1%) of patients developed uveitis 57 had oligoarticular JIA • 30 (52.6%) developed uveitis within 6 months of disease onset • 45 (78.9%) developed uveitis within 2 years of disease onset • 52 (91.2% developed uveitis within 4 years of disease onset • 3 patients developed uveitis after 8.2, 9, and 11.7 years disease onset 3 had polyarticular JIA and uveitis was present at onset of disease 2 had systemic JIA and uveitis developed after 7 and 8.2 years 22/62 (35.5%) of patients developed ocular complications
Chia 2003[7]	Case Control	1986-2000 (1986-1993 screening period one and 1994-2000 screening period two which correspon ded to the time	409 patients with JRA (299 oligo, 110 other) of which 126 were diagnosed with uveitis during the study period excluded patients (ERA, sJIA, seropositive	Screening at initial ophthalmology visit and follow-ups based on guidelines of Kanski (1989), which specified the following screening intervals for different JIA subtypes: Systemic: annual Polyarticular: every 6 months Pauciarticular: every 3 months Positive ANA: every 2 months	126 patients developed uveitis during the study period. 104 were considered mild and 22 were considered severe. 35 of these patients were diagnosed at the initial eye exam. 12/35 (34%) were classified as severe at diagnosis compared to 10/91 (11%) diagnosed as severe at follow-up (p =0.002). The proportion of male patients among those with severe uveitis at diagnosis was significantly higher 12/22 patients (55% OR 3.5, p = 0.006) AND the proportion of those with severe uveitis who were male was greater than those with mild or no uveitis that were male (OR 6.1, p =0.001).

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
		period after American guidelines published)	JIA, and those whose first presentation was uveitis		Those with severe uveitis at diagnosis had shorter intervals to diagnosis of uveitis compared to those with mild uveitis (p 0.001) and were older at the onset of arthritis symptoms (p =0.01)
Kodsi 2002[6]	Retrospective Cohort	Aug 1984-July 2001	158 patients with JRA (105 pauci, 21 poly, 9 systemic, 23 diagnosis not available)	Screening criteria based on classification of JRA Pauci or poly onset less than 7 years of age and ANA positive = 3 mo Pauci or poly onset, ANA negative regardless of age = 6 mo High risk with normal exam for 4 years (first group above) = 6 mo Systemic onset =12 mo Pauci or poly onset less than 7yo of age and normal eye exam for 7 yo = 12 mo 7 years or older at diagnosis and normal eye exam for 4 years =12 mo	39/158 developed uveitis (39%). 16/39 had uveitis on the first eye exam When uveitis was absent on the first eye exam, the mean time to develop it was 20 months (range 4-81 months). Increased risk of uveitis associated with pauciarticular JRA 34/39 patients with this category ($p<0.0005$) 29/39 (75%) of patients with uveitis had a positive ANA ($p<0.0005$). Ocular complications occurred in 8/39 patients (20.5%).

References

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PICO 2. In children and adolescents with JIA with inactive uveitis on stable therapy, what are the benefits and harms of ophthalmologic monitoring no longer than every 3 months until tapering compared to monitoring less frequently than every 3 months?

Summary: The literature searches identified two studies that measured monitoring of uveitis reoccurrence. In one study[1] the estimated probability of a uveitis reactivation by monitoring every three months was 2.5% by three months (95% CI: 0%-16.8%), 18.4% by 6 months (95% CI: 9.2-34.9%), and 21.3% by 9 months (95% CI 11.2-38.1%), and by 12 months was 24.4% (95% CI 9.7, 53.5%). Another study[2] concluded that "On the basis of our results, ophthalmologic controls every 3 months for the first 6 years from the first uveitis episode would confirm diagnosis of uveitis relapses in almost 70% of the patients with antecedent uveitis episodes." In this latter study, 29% of patients clearly had stable uveitis; it is unclear whether additional patients achieved stability at longer follow-up.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring conducted on relevant population	Results
1331, Lerman M., 2015 [1]	Retrospective cohort study	12 months	50 patients with risk of development of uveitis under TNFi treatment	The probability of a uveitis reactivation was estimated at 3, 6, 9 and 12 months	Among the 39 subjects who achieved quiescence, the estimated proportion of those in whom uveitis reactivated within 12 months of quiescence was 27.8% (95% CI: 15.9-45.8%). The estimated probability of a uveitis reactivation was 2.5% by three months (95% CI: 0%-16.8%), 18.4% by 6 months (95% CI: 9.2-34.9%), and 21.3% by 9 months (95% CI 11.2-38.1%). For only those 20 subjects who continued on anti-TNFα, the estimated probability of a uveitis reactivation by 12 months was 24.4% (95% CI 9.7, 53.5%), and the estimated median time to failure was 20.5 months (32.1 patient-years).
1751 Grassi 2007 [2]	Retrospective cohort	Follow up: 7.6 +/- 5.6 years Age at JIA onset: 4.9 y/o +/- 3.6 years	309 patients	All patients had slit-lamp examinations every 3 to 6 months to assess the presence of uveitis and complications.	62/309 (20.1%) of patients developed uveitis 57 had oligoarticular JIA • 30 (52.6%) developed uveitis within 6 months of disease onset • 45 (78.9%) developed uveitis within 2 years of disease onset • 52 (91.2% developed uveitis within 4 years of disease onset • 3 patients developed uveitis after 8.2, 9, and 11.7 years disease onset 3 had polyarticular JIA and uveitis was present at onset of disease 2 had systemic JIA and uveitis developed after 7 and 8.2 years 18/62 (29%) of patients had only a single episode of uveitis. The remaining 71% had repeated episodes.

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring conducted on relevant population	Results
					22/62 (35.5%) of patients developed ocular complications The authors concluded "On the basis of our results, ophthalmologic controls every 3 months for the first 6 years from the first uveitis episode would confirm diagnosis of uveitis relapses in almost 70% of the patients with antecedent uveitis episodes. Nevertheless, longer uveitis relapses can occur beyond these time bounds."

References:

1. Lerman M. et al. Uveitis Reactivation in Children Treated with Tumor Necrosis Factor-α Inhibitors. Am J Ophthalmol. 2015 July; 160(1): 193–200.e1. doi:10.1016/j.ajo.2015.04.016.
2. Grassi A. et al. Prevalence and Outcome of Juvenile Idiopathic Arthritis-Associated Uveitis and Relation to Articular Disease, J Rheumatol 2007; 34;1139-1145

PICO 3. In children and adolescents with JIA with inactive uveitis who are tapering or discontinuing therapy, should ophthalmologic monitoring within 1 month after each change of topical steroid therapy versus monitoring less frequently be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 4. In children and adolescents with JIA with inactive uveitis who are tapering or discontinuing therapy, should ophthalmologic monitoring 2 months after each change of systemic therapy versus monitoring less frequently be recommended?

Summary. One retrospective cohort study indirectly addressed this question. The study performed monitoring every three months and did not compare to monitoring every two months. See results in table below.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring conducted to relevant population	Results
1331, Lerman M., 2015 [1]	Retrospective cohort study	12 months	50 patients with risk of development of uveitis under TNFi treatment and discontinuation	The probability of a uveitis reactivation was estimated at 3, 6, 9 and 12 months	Among the 39 subjects at risk of the primary outcome, the estimated proportion of those in whom uveitis reactivated within 12 months of quiescence was 27.8% (95% CI: 15.9-45.8%). The estimated probability of a uveitis reactivation was 2.5% by three months (95% CI: 0%-16.8%), 18.4% by 6 months (95% CI: 9.2-34.9%), and 21.3% by 9 months (95% CI 11.2-38.1%). Among only those who continued on anti-TNFα, the estimated probability of a uveitis reactivation by 12 months was 24.4% (95% CI 9.7, 53.5%), and the estimated median time to failure was 20.5 months (32.1 patient-years). The estimated proportion whose uveitis reactivated within 12 months of discontinuing anti-TNFα was much higher (63.8%, 95% CI: 38.9-87.7%). The estimated probability of a uveitis reactivation was 17.9% by three months (95% CI: 6.1%-46.6%), 38.0% by 6 months (95% CI: 19.0-66.1%), and 54.8% by 9 months (95% CI 31.4-81.2%); the median time to failure was 3.9 months (range 6.9-23.7 months).

References:

1. Lehman M., Uveitis Reactivation in Children Treated with Tumor Necrosis Factor-α Inhibitors. Am J Ophthalmol. 2015 July; 160(1): 193–200.e1. doi:10.1016/j.ajo.2015.04.016.

PICO 5. In children and adolescents with JIA with active CAU in which therapy is being changed/escalated, should ophthalmologic monitoring visits no longer than every 2 weeks versus monitoring less frequently than every 2 weeks the appropriate frequency of ophthalmologic monitoring be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 6. In children and adolescents with JIA with chronic uveitis controlled who have achieved control of their uveitis on systemic therapy and 1-2 drops/day of prednisolone acetate 1% (or equivalent), should weaning topical steroids first versus weaning systemic therapy first be recommended?

Summary: Two retrospective cohort studies provided indirect evidence to address this question. Kothari et al.[1] found that topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis; the risk increased with increasing number of drops/day. In contrast, systemic corticosteroid use was not significantly associated with elevated IOP after adjustment for other factors in multivariate analyses. Another retrospective cohort study found that ≤ 3 drops daily of prednisone is preferred to ≥ 4 drops daily in order to decrease the risk of developing cataracts.[2]

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7152 Kothari 2015[1]	Retrospective cohort study	Enrollment 29 years, follow-up 2 years	1593 eyes of 916 children with non-infectious uveitis	Risk factor study that included treatment among factors evaluated. Treatments included topical corticosteroids and systemic corticosteroids.	Topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis. The hazard ratio increased with number of drops/day. Systemic corticosteroid use was not significantly associated with risk of elevated IOP after adjusting for other factors in multivariate analysis.
1621 Thorne 2010 [1]	Retrospective Cohort Study	21 years	60 eyes of 40 patients with JIA-Uveitis	Topical prednisone	≤ 2 drops daily: incidence of cataract 0/eye-year (95% CI 0-0.03 ey) 3 drops daily: incidence of cataract 0.01/eye-year (95% CI 0.005-0.03 ey)

			Median age at diagnosis of uveitis 7 (range 1-36)		4 drops daily: incidence of cataract 0.07/eye-year (95% CI 0.02-0.14 ey) >4 (5-12) drops daily: incidence of cataract 0.16/eye-year (95% CI 0.09-0.21 ey) Use of ≤ 3 drops daily was associated with an 87% reduction in the risk of new onset cataract when compared to ≥ 4 drops daily (RR = 0.13, 95% CI: 0.02- 0.69, P = 0.02).

References

1. Kothari S, Foster S, Pistilli M, Liesegang TL, Daniel E, Sen HN, et al. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. Amer Acad Ophthalmol 2015;122:1987-2001.

2. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436-1441.

PICO 7. In children and adolescents with JIA with chronic uveitis controlled on (but still requiring) 1-2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months, not on systemic therapy, should adding systemic therapy in order to taper topical steroids versus not adding systemic therapy and maintaining on topical steroids be recommended?

Summary: Two retrospective cohort studies provided indirect evidence to address this question. Kothari et al.[1] found that topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis; the risk increased with increasing number of drops/day. In contrast, systemic corticosteroid use was not significantly associated with elevated IOP after adjustment for other factors in multivariate analyses. Another retrospective cohort study found that ≤ 3 drops daily of prednisone is preferred to ≥ 4 drops daily in order to decrease the risk of developing cataracts.[2]

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7152 Kothari 2015[1]	Retrospective cohort study	Enrollment 29 years, follow-up 2 years	1593 eyes of 916 children with non-infectious uveitis	Risk factor study that included treatment among factors evaluated. Treatments included topical corticosteroids and systemic corticosteroids.	Topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis. The hazard ratio increased with number of drops/day. Systemic corticosteroid use was not significantly associated with risk of elevated IOP after adjusting for other factors in multivariate analysis.
1621 Thorne 2010 [1]	Retrospective Cohort Study	21 years	60 eyes of 40 patients with JIA-Uveitis Median age at diagnosis of uveitis 7 (range 1-36)	Topical prednisone	≤ 2 drops daily: incidence of cataract 0/eye-year (95% CI 0-0.03 ey) 3 drops daily: incidence of cataract 0.01/eye-year (95% CI 0.005-0.03 ey) 4 drops daily: incidence of cataract 0.07/eye-year (95% CI 0.02-0.14 ey) >4 (5-12) drops daily: incidence of cataract 0.16/eye-year (95% CI 0.09-0.21 ey) Use of ≤ 3 drops daily was associated with an 87% reduction in the risk of new onset cataract when compared to ≥ 4 drops daily (RR = 0.13, 95% CI: 0.02- 0.69, P = 0.02).

References

1. Kothari S, Foster S, Pistilli M, Liesegang TL, Daniel E, Sen HN, et al. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. Amer Acad Ophthalmol 2015;122:1987-2001.

2. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436-1441.

PICO 8. In children and adolescents with JIA with chronic uveitis controlled on (but still requiring) 1-2 drops/day of prednisolone acetate 1% (or equivalent), also on systemic therapy, should changing/escalating systemic therapy versus not changing systemic therapy and maintaining current therapy be recommended?

Summary: Two retrospective cohort studies provided indirect evidence to address this question. Kothari et al.[1] found that topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis; the risk increased with increasing number of drops/day. In contrast, systemic corticosteroid use was not significantly associated with elevated IOP after adjustment for other factors in multivariate analyses. Another retrospective cohort study found that ≤ 3 drops daily of prednisone is preferred to ≥ 4 drops daily in order to decrease the risk of developing cataracts.[2]

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7152 Kothari 2015[1]	Retrospective cohort study	Enrollment 29 years, follow-up 2 years	1593 eyes of 916 children with non-infectious uveitis	Risk factor study that included treatment among factors evaluated. Treatments included topical corticosteroids and systemic corticosteroids.	Topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis. The hazard ratio increased with number of drops/day. Systemic corticosteroid use was not significantly associated with risk of elevated IOP after adjusting for other factors in multivariate analysis.
1621 Thorne 2010 [1]	Retrospective Cohort Study	21 years	60 eyes of 40 patients with JIA-Uveitis Median age at diagnosis of uveitis 7 (range 1-36)	Topical prednisone	≤ 2 drops daily: incidence of cataract 0/eye-year (95% CI 0-0.03 ey) 3 drops daily: incidence of cataract 0.01/eye-year (95% CI 0.005-0.03 ey) 4 drops daily: incidence of cataract 0.07/eye-year (95% CI 0.02-0.14 ey) >4 (5-12) drops daily: incidence of cataract 0.16/eye-year (95% CI 0.09-0.21 ey) Use of ≤ 3 drops daily was associated with an 87% reduction in the risk of new onset cataract when compared to ≥ 4 drops daily (RR = 0.13, 95% CI: 0.02- 0.69, P = 0.02).

References

1. Kothari S, Foster S, Pistilli M, Liesegang TL, Daniel E, Sen HN, et al. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. Amer Acad Ophthalmol 2015;122:1987-2001.

2. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436-1441.

PICO 9. In children and adolescents with JIA with chronic active uveitis, irrespective of use of topical or systemic therapy, should giving intraocular steroid injections versus not giving intraocular steroid injections be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 10. In children and adolescents with JIA with chronic active uveitis, should treatment with prednisolone acetate 1% topical drops versus difluprednate topical drops be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 11. **In children and adolescents with JIA** with active CAU, should adding systemic steroids to topical steroid therapy for short term control versus not adding systemic steroids, which may include increasing frequency of topical steroids, be recommended?

Summary. Our searches identified one retrospective cohort study with 55 patients with JIA and uveitis that addressed this question.[1] As shown in the table below, among patients with mild uveitis on initial examination, eyes receiving high-dose systemic corticosteroids (CS) had a significantly higher risk of developing cataracts compared to patients receiving low-dose (p=0.0023) or no systemic CS (p=0.001). Although the risk of developing glaucoma was not significantly elevated in patients receiving high-dose CS, the findings are imprecise due to the low number of patients and events. Therefore, the possibility of an elevated risk of glaucoma cannot be ruled out.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2209, Wolf 1987 [1]	Retrospective Cohort	1960-1985	55 patients with JRA and uveitis followed for at least 1 year Poly, Oligo, and sJRA included Ankylosing spondylitis patients were excluded	Systemic corticosteroids (CS) were used in patients with a total of 32 eyes with mild uveitis on initial examination. 27 were receiving systemic low dose CS for arthritis therapy, and 5 received high dose CS for control of contralateral uveitis.	Cataracts: All 5 eyes receiving high-dose CS developed cataracts (100%) versus 6/27 (22%) of eyes in patients receiving low-dose CS and 2/16 (13%) eyes in patients not treated with systemic CS. The differences between high-dose and low-dose CS (p=0.0023) and high-dose and no CS (p=0.001) are statistically significant. Glaucoma: Glaucoma developed in 2/5 (40%) eyes in receiving high-dose CS, 3/27 (11%) of eyes in patients receiving low-dose CS, and 2/16 (13%) eyes in patients not treated with systemic CS. These differences were not statistically significant, but the low number of events means the findings are imprecise.

References

1. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology. 1987;94(10):1242-1248.

PICO 12. In children and adolescents with JIA with new uveitis activity (either no prior uveitis or uveitis that was previously controlled, no active arthritis, and no topicals currently) regardless of current systemic therapy, should topical steroid therapy only and changing/escalating systemic therapy if unable to taper versus topical steroid therapy and changing/escalating systemic therapy immediately be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 13. In children and adolescents with JIA with active CAU regardless of joint disease (assume uveitis guides therapy), should methotrexate PO versus methotrexate SQ be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 14: In children and adolescents with JIA starting a systemic medication for their arthritis with no history of uveitis, what are the benefits and harms of etanercept compared to other TNFi in influencing the incidence of uveitis?

Summary: The literature search identified no RCTs that compared etanercept to another TNFi in regards to the incidence of new onset uveitis. Four observational studies provided direct and indirect evidence of etanercept compared to other TNFi and DMARDs regarding uveitis occurrence. One study[1] that directly compared etanercept (ETA) to adalimumab (ADA) found no significant difference in uveitis events in the ADA group compared to the ETA group (Table 1). However, this included all uveitis events and not just new onset. The ADA group in this study had no new onset uveitis events after starting ADA. In this same study, the ETA + MTX group had fewer uveitis events compared to the ADA + MTX group, but the difference was not statistically significant (Table 2). Again, however, this included all uveitis events and not just new onset which is the PICO question of interest. A second study[2] found no statistically significant difference in the risk of development of uveitis with or without TNFi (mostly ETA in the study)(Table 3). Two other observational studies[3,4] found lower incidences of uveitis in patients treated with MTX or a combination of MTX and ADA compared to ETA (Table 4). One study[4] found increased rates of infection in patients on TNFi but no increased rate of malignancy compared to methotrexate.

Quality of Evidence across all critical outcomes: Very Low

Table 1. ETA compared to ADA in Juvenile Idiopathic Arthritis Patients: MTX vs ETA vs ETA + MTX vs ADA vs ADA +MTX

Bibliography: Foeldvari I, Becker I, Horneff G. Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken). 2015;67(11):1529-1535.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With ADA	With ETA		Risk with ADA	Risk difference with ETA
uveitis occurrence											

623 (1 observational study) [a]	very serious [a,b]	not serious	not serious	serious [c]	all plausible residual confounding would suggest spurious effect, while no effect was observed	◯◯◯ VERY LOW	7/148 (4.7%)	17/475 (3.6%)	**OR 0.75** (0.30 to 1.84)	47 per 1,000	**11 fewer per 1,000** (33 fewer to 36 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Retrospective cohort study. Study design very vulnerable to selection bias.

b. The authors also commented that it was surprising that there were lower number of events in the ETA vs ADA group and explained that this could have been due to selection bias "patients with previous uveitis are 3x more likely to have received ADA. Consequently, the ADA subgroup may have more aggressive disease compared to the ETA group at baseline. In addition, contradicting the results, there were no first time uveitis events in the ADA mono therapy group. This could cause enbrel to appear to have a more protective effect compared to ADA.

c. Concern for imprecision given the low number of uveitis event rates and wide confidence interval that crosses the line of no difference.

Table 2. ETA + MTX compared to ADA + MTX in Juvenile Idiopathic Arthritis Patients: MTX vs ETA vs ETA + MTX vs ADA vs ADA +MTX

Bibliography: Foeldvari I, Becker I, Horneff G. Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken). 2015;67(11):1529-1535.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ADA + MTX	**With ETA + MTX**		**Risk with ADA + MTX**	**Risk difference with ETA + MTX**

Table 2. ETA + MTX compared to ADA + MTX in Juvenile Idiopathic Arthritis Patients: MTX vs ETA vs ETA + MTX vs ADA vs ADA +MTX

Bibliography: Foeldvari I, Becker I, Horneff G. Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken). 2015;67(11):1529-1535.

Quality assessment							Summary of findings				
uveitis occurence											
1441 (1 observational study)	very serious [a,b]	not serious	not serious	serious [c]	all plausible residual confounding would suggest spurious effect, while no effect was observed	◯◯◯ VERY LOW	6/216 (2.8%)	20/1225 (1.6%)	**OR 0.58** (0.23 to 1.46)	28 per 1,000	**11 fewer per 1,000** (21 fewer to 12 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Retrospective cohort study. Study design very vulnerable to selection bias.

b. The authors also commented that it was surprising that there were lower number of events in the ETA vs ADA group and explained that this could have been due to selection bias "patients with previous uveitis are 3x more likely to have received ADA. Consequently, the ADA subgroup may have more aggressive disease compared to the ETA group at baseline. In addition, contradicting the results, there were no first time uveitis events in the ADA mono therapy group. This could cause enbrel to appear to have a more protective effect compared to ADA.

c. Concern for imprecision. small number of uveitis events, wide 95% CI overlaps with line of no difference.

Table 3. TNFi compared to no TNFi in Juvenile Idiopathic Arthritis Patients in regards to uveitis onset.

Bibliography: Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr. 2006;149(6):833-836.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no TNFi	**With TNFi**		**Risk with no TNFi**	**Risk difference with TNFi**
New uveitis while on TNFi (ETN) vs no TNFi											
1058 (1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	◯◯◯ VERY LOW	22/988 (2.2%)	2/70 (2.9%)	**RR 1.28** (0.31 to 5.35)	22 per 1,000	**6 more per 1,000** (15 fewer to 97 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Retrospective cohort, non-randomized study

b. Does not directly answer the PICO question that asks how does ETA compare to other TNFi. In this study, ETA is compared to a placebo.

c. Imprecision a concern due to small number of events in both groups and wide 95% CI that crosses line of no difference.

Table 4. Additional Data from Other Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Tappeiner 2016[3]	Retrospective Comparative Cohort Study	Jan 2002-Dec 2013	Data extracted from the National Paediatric Rhumatological Database in Germany **Inclusion**	MTX vs TNFi vs combo of MTX + TNFi **Outcome:** Incidence uveitis following anti-inflammatory treatment for arthritis	Discrete time to survival analysis was used to assess the impact of disease activity, MTX, TNF inhibitor therapy on uveitis onset 3512 patients with JIA fulfilled the inclusion criteria. Uveitis developed in 180 (5.1%) patients within 1 year after arthritis onset (of note, due to study follow-up every 1 year, could not tell if MTX/TNF were started before or after uveitis onset at the first year of follow-up)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			criteria: JIA patients with disease duration <12 months at entry and >/= to 2 year follow-up	Patients were assessed annually during the study period for the outcome of interest and other disease activity	Uveitis developed in another 251 patients (7.1%) after the first year of follow-up. From this group: MTX/TNFi treatment reduced the incidence of uveitis as follows in this group compared to those not on MTX/TNFi or a combo of the two after adjusting for ANA status, ILAR category, age at JIA onset, JADAS-10, and disease duration: • MTX: HR 0.63 p =0.022 • TNFi: HR = 0.56 p <0.001 • MTX + TNFi: HR 0.10 p <0.001 *TNF only group (38 etanercept, 5 adalimumab, 5 other) *TNF + MTX (362 etanercept, 65 adalimumab, 9 infliximab) ***Incidence of Uveitis with MTX + adalimumab was 1.4% compared to 5.9% for MTX + etanercept. Patients treated with MTX in the first year had HR 0.29 p<0.001 compared to HR of MTX 0.63 (see above) in patients that did not start MTX in the first year
Klotsche 2016[4]	Retrospective Comparative Cohort Biker and Jumbo registry (ongoing prospective cohort registries)	Jan 1st 2001- Dec 31 2012 2005-2011 MTX only group	Children with JIA with a polyarticular course, sJIA, ERA, and psoriatic JIA	Adalimumab vs etanercept vs MTX Outcome: Longterm safety of MTX, ADA, and ETA Measured Outcomes: Relative Risks of SAE (Serious Adverse Events) ESI (Events of Special Interest)	More than 40% poly JIA course (36% RF+ 8% RF-) Total patients ever exposed to the following drugs: ETA (n =1414) ADA (n =320) MTX (n =1455) Risk assessment started with first exposure. Significantly more SAE, infections, and medically important infections observed for: ETA: 4.5, 5.7, 0.9; ADA 4.7, 11.4, 0.4 per 100 exposure years) compared to those treated with (MTX: 2.6, 5.5, 0.5 per 100 exposure years) The risk for malignancy was not significantly different for ETA and ADA compared to MTX (0.09, 0.27, and 0.07 per 100 years) Patients under ETA monotherapy developed more incidental IBD and uveitis (0.5, 0.8/100 exposure years) compared to Enbrel + MTX (0.1, 0.2/100 exposure years) or MTX alone (0.03, 0.1/100 exposure years) this may be due to inadequate response vs paradoxical effect.

References

1. Foeldvari I, Becker I, Horneff G. Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken). 2015;67(11):1529-1535.
2. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr. 2006;149(6):833-836.
3. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J. Impact of Antiinflammatory Treatment on the Onset of Uveitis in Juvenile Idiopathic Arthritis: Longitudinal Analysis From a Nationwide Pediatric Rheumatology Database. Arthritis Care Res (Hoboken). 2016;68(1):46-54.
4. Klotsche J, Niewerth M, Haas JP, Huppertz HI, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75(5):855-861.

PICO 15. In children and adolescents with JIA with active arthritis and active CAU, what are the benefits and harms of starting etanercept compared to any other medication like methotrexate, other TNFi or other biologics?

Summary: One small retrospective observational study directly addressed this PICO question.[1] The study compared uveitis activity change at 24 months, uveitis remission, and serious adverse events in patients receiving etanercept or infliximab. Although no significant differences were found between treatment groups at 24 months, the findings were imprecise due to the low number of patients and wide 95% CIs that cross the line of no difference. In addition, a very small RCT (12 patients) indirectly addressed the question by comparing the efficacy of etanercept to placebo in 12 patients with JIA and active CAU. Although the study found no significant between-group difference in number of treatment "successes" at 6 months (during the double-blind phase), the study was not adequately powered to detect a difference. Because of this and the study's indirectness, it was rated as very low quality evidence.

Quality of evidence across all critical outcomes: Very Low

IFX compared to ETN for JIA children with Uveitis

Bibliography: Tynjala, P., et al. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 2007;66(4), 548-550.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With ETN	With IFX		Risk with ETN	Risk difference with IFX
Uveitis activity change at 24months											
45 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	9/21 (42.9%)	5/24 (20.8%)	**OR 0.35** (0.09 to 1.30)	429 per 1,000	**221 fewer per 1,000** (365 fewer to 65 more)
Uveitis remission											

IFX compared to ETN for JIA children with Uveitis

Bibliography: Tynjala, P., et al. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 2007;66(4), 548-550.

Quality assessment							Summary of findings				
45 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	1/21 (4.8%)	4/24 (16.7%)	**OR 4.00** (0.41 to 39.00)	48 per 1,000	**119 more per 1,000** (28 fewer to 613 more)
SAEs											
45 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	3/21 (14.3%)	4/24 (16.7%)	**OR 1.20** (0.24 to 6.10)	143 per 1,000	**24 more per 1,000** (104 fewer to 361 more)

CI: Confidence interval; O**R:** Odds ratio

Explanations

a. Observational study

b. Wide CI crossing both significant and non-significant effect thresholds

Table 2. RCT Comparing Etanercept to Placebo

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1833, Smith 2005	Randomized controlled trial	6 months (double-blind phase); open-label (all patients received ETN) after 6 months and out to 12 months.	12 patients with JIA and active CAU	Etanercept (7 patients), Placebo (5 patients). In addition, all patients received corticosteroids and 7/12 patients (3/7 in ETN group and 4/5 in placebo group) received MTX.	Success at 6 months: ETN 3/7 patients, placebo 2/5, p>0.50. No serious AEs occurred during the trial.

References

1. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis. 2007;66(4):548-550.
2. Smith J, Thompson D, Whitcup S, Suhler E, Clarke G, Smith S et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arth Rheum 2005;53(1):18-23.

PICO 16. In children and adolescents with JIA with inactive uveitis, off of topical steroids and needing a change in systemic therapy for active arthritis, should starting etanercept versus another TNFi be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 17: In children and adolescents with JIA with active CAU regardless of joint disease (assume uveitis guides therapy), what are the benefits and harms of adalimumab compared to infliximab as first choice TNFi?

Summary**.** One RCT[1] and two observational studies[2, 3] addressed this PICO question. The RCT[1] compared adalimumab to placebo and is included only as indirect evidence (Table 1). It reported significantly fewer treatment failures in the adalimumab arm (RR=0.44, CI 0.27-0.74). The adalimumab arm showed a higher rate of serious adverse events (RR=2.83) than placebo but the finding was imprecise due to a wide 95% confidence interval. The observational studies[2, 3] directly compared infliximab to adalimumab, both of them measured remission, and one study measured recurrent uveitis course (Table 2). The remission rate favored adalimumab over infliximab (RR 2.04, 95% CI 1.34 to 3.10) while the recurrent uveitis course was imprecise (RR 0.72, 95% CI 0.38 to 1.37).

Quality of evidence across all critical outcomes: Very low

Table 1. Adalimumab compared to Placebo for JIA children with active CAU

Bibliography: Ramanan A. et al., Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis, N Engl J Med 2017;376:1637-46.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Adalimumab		Risk with Placebo	Risk difference with Adalimumab
Treatment failures											
90 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	18/30 (60.0%)	16/60 (26.7%)	**RR 0.44** (0.27 to 0.74) **Favors Ada**	600 per 1,000	**336 fewer per 1,000** (438 fewer to 156 fewer)
SAE											

Table 1. Adalimumab compared to Placebo for JIA children with active CAU

Bibliography: Ramanan A. et al., Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis, N Engl J Med 2017;376:1637-46.

Quality assessment							Summary of findings				
90 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/30 (10.0%)	17/60 (28.3%)	**RR 2.83** (0.90 to 8.92)	100 per 1,000	**183 more per 1,000** (10 fewer to 792 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Comparison to placebo

b. Wide CI that crosses both significant and non-significant effect lines

Table 2. Adalimumab compared to Infliximab for JIA children with active CAU

Bibliography: Zannin M. et al. Safety and Efficacy of Infliximab and Adalimumab for Refractory Uveitis in Juvenile Idiopathic Arthritis: 1-year Followup Data from the Italian Registry, J Rheumatol 2013;40;74-79.
Simonini G. et al. Prevention of Flare Recurrences in Childhood-Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab, Arthritis Care & Research, Vol. 63, No. 4, April 2011, pp 612–618.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Infliximab	**With Adalimumab**		**Risk with Infliximab**	**Risk difference with Adalimumab**
Remission											

Table 2. Adalimumab compared to Infliximab for JIA children with active CAU

Bibliography: Zannin M. et al. Safety and Efficacy of Infliximab and Adalimumab for Refractory Uveitis in Juvenile Idiopathic Arthritis: 1-year Followup Data from the Italian Registry, J Rheumatol 2013;40;74-79.
Simonini G. et al. Prevention of Flare Recurrences in Childhood-Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab, Arthritis Care & Research, Vol. 63, No. 4, April 2011, pp 612–618.

Quality assessment							Summary of findings				
111 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	19/57 (33.3%)	36/54 (66.7%)	**RR 2.04** (1.34 to 3.10) **Favors Ada**	333 per 1,000	**347 more per 1,000** (113 more to 700 more)
Recurrent Uveitis Course											
91 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	17/48 (35.4%)	11/43 (25.6%)	**RR 0.72** (0.38 to 1.37)	354 per 1,000	**99 fewer per 1,000** (220 fewer to 131 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. observational study

b. Wide CI that crosses both significant and non-significant effect lines

References:

1. Ramanan A. et al., Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis, N Engl J Med 2017;376:1637-46.
2. Zannin M. et al. Safety and Efficacy of Infliximab and Adalimumab for Refractory Uveitis in Juvenile Idiopathic Arthritis: 1-year Followup Data from the Italian Registry, J Rheumatol 2013;40;74-79
3. Simonini G. et al. Prevention of Flare Recurrences in Childhood-Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab, Arthritis Care & Research, Vol. 63, No. 4, April 2011, pp 612–618.

PICO 18. In children and adolescents with JIA with active CAU regardless of joint activity, should above standard dosing of infliximab (>10 mg/kg/dose every 4 weeks) versus standard JIA dosing be recommended?

Summary: The literature searches identified one retrospective observational study (a case series with 17 patients) that addressed this PICO question. Although a higher infliximab dose generally resulted in faster achievement of inactive uveitis, this comparison was based on very few patients (particularly in the lower dose group). See Results in table below.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1788, Kahn P, 2006	Retrospective observational study (case series)	3 years	17 children with chronic uveitis (10 with JIA as the cause of uveitis)	Infliximab 10-20 mg/kg (1 patient started at 5 mg/kg but eventually received 13 mg/kg every 4 weeks)	Thirteen patients (76%) had no detectable intraocular inflammation 1 to 2 weeks after the first or second infusion (12 were on 20 mg/kg and 1 was on 15 mg/kg q4weeks). The 4 remaining patients required 3 to 7 infusions to attain quiescent disease. These 4 patients were started on lower initial doses of infliximab: 10 mg/kg every 3 weeks (patient 6), 10 mg/kg every 4 weeks (patients 11 and 15), and 5 mg/kg every 4 weeks (patient 13).

References

1. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Opthalmol. 2006;113:860-864.

PICO 19. In children and adolescents with JIA with active CAU regardless of joint activity, should above standard dosing of adalimumab (double dosing every 2 weeks or weekly dosing) versus standard JIA dosing be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 20. In children and adolescents with JIA with active CAU on TNFi at standard JIA dose regardless of joint disease (assume uveitis guides therapy) who have failed one TNFi at standard dose, should escalating dose and/or frequency to above-standard dose versus switching to another TNFi be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 21. In children and adolescents with JIA with active CAU who have failed first TNFi, regardless of arthritis activity (assume uveitis guides therapy), should switching to another TNFi versus switching to a biologic in another category be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 22. In children and adolescents with JIA with severe active uveitis (2+ cells or more, or 1+ cells AND complications), should starting on MTX and a TNFi immediately versus methotrexate being trialed alone first be recommended?

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

Quality of evidence across all critical outcomes: Very low

PICO 23. In children and adolescents with JIA with active CAU, who have failed TNFi (one or more), should abatacept versus any other medication be recommended?

Summary: Three case-series studies addressed this PICO question. In all studies patients refractory or intolerant to TNFi agents received abatacept. The study duration varied from 9.2 to 12 months. The inactivity rate varied from 48% (10 out of 21 patients)[1] to 86% (6 out of 7 patients)[3]. The frequency of uveitis flares reduced in one study from 3.7 to 1.2 when treated with abatacept as a second line treatment[2], and in another study from 3.7 to 0.7[3]. No ocular complications occurred in one study[3], 3 out of 21 patients developed new ocular complications in another study[1], and the number of complications changed from 10 to 15 among 17 patients when abatacept was used as a second line drug in the remaining study[2]. The efficacy of ABA was greater after the first 6 months of treatment; only 9/24 uveitis flares (37.5%) occurred during the second semester[2]. There was improvement of arthritis in most patients (50%[1], 61%[2] to 86%[3], and no patient without articular involvement at baseline developed arthritis during the follow-up.

Quality of evidence: Very Low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1342, Tappeiner C., 2015	Case-series	12 months	21 JIA patients (16 female) with active uveitis (n = 21) and arthritis (n = 18)	Abatacept	Out of 21 patients, uveitis inactivity was achieved in 11 patients, but recurred later in 8 of them, and remained active in another 10 cases. Ocular complications secondary to uveitis were present in 17 patients at baseline, while 3 patients developed new ocular complications during follow-up. In 7 of them articular inactivity was achieved by the end of follow-up. In another 2 patients with joint inactivity at baseline, arthritis remained inactive during the study. No adverse events were reported that were due to ABA treatment.
1193 Birolo C., 2016	Case-series	12 months	Thirty-five patients with JIA-associated uveitis refractory to TNFi agents.	Abatacept, 14 patients with ABA as a first-line biological agent (ABA-1), 17 patients with ABA as a second-line treatment	17 (54.8%) had clinical remission. Preexisting ocular complications improved or remained stable in all but 5 patients, all in the ABA-2 group. The mean value in ABA-1 group changed in uveitis flares from 4.1 to 1.2, No. complications have not changed. For ABA-2 group, the mean value for uveitis flares changed from 3.7 to 1.2, for No. complications from 10 to 15. The efficacy of ABA was greater after the first 6 months of treatment — only 9/24 uveitis flares (37.5%) occurred during the second semester. Arthritis went into clinical remission in 11/18 patients (61.1%; 5/11 ABA-1 and 6/7 ABA-2). In the remaining 7 patients, the median number of active joints decreased from 10.1 to 7.0. No patient without articular involvement at baseline (3 in ABA-1 and 10 in ABA-2) developed arthritis during the follow-up.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1623, Zulian F., 2010	Case-series	Mean duration of 9.2 months	Seven patients with severe JIA–related uveitis, refractory or intolerant to anti-TNF agents	Intravenous abatacept (10 mg/kg monthly)	Out of 7 patients 6 maintained a clinical remission after a mean of 9.2 months of treatment. The mean frequency of uveitis flares during the 6 months before and after treatment decreased from 3.7 to 0.7 episodes. No new ocular complications or worsening of preexisting ones were reported. During the follow-up, arthritis went into remission in 5 patients, and improved in 1 patient (patient 7) but persisted to be slightly active.

References:

1. Tappeiner, C., Miserocchi, E., Bodaghi, B., Kotaniemi, K., Mackensen, F., Gerloni, V., et al. (2015). Abatacept in the Treatment of Severe, Longstanding, and Refractory Uveitis Associated with Juvenile Idiopathic Arthritis. The Journal of Rheumatology, 42(4), 706-711. doi:10.3899/jrheum.140410
2. Birolo, C., Zannin, M. E., Arsenyeva, S., Cimaz, R., Miserocchi, E., Dubko, M., et al. (2016). Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis. The Journal of Rheumatology, 43(11), 2068-2073. doi:10.3899/jrheum.151389
3. Zulian, F., Balzarin, M., Falcini, F., Martini, G., Alessio, M., Cimaz, R., et al. (2010). Abatacept for severe anti–tumor necrosis factor α refractory juvenile idiopathic arthritis–related uveitis. Arthritis Care & Research, 62(6), 821-825. doi:10.1002/acr.20115

PICO 24. In children and adolescents with JIA with active CAU, who have failed TNFi (one or more), should tocilizumab versus any other medication be recommended?

Summary: Two retrospective uncontrolled observational studies indirectly addressed this question. In both studies, all patients received tocilizumab. Calvo-Rio et al. showed increased improvement in uveitis over time with 3 patients having serious adverse events.[1] Tappeiner et al. showed an increasing percentage of patients with uveitis inactivity with prolonged tocilizumab treatment. Four patients had new ocular complications.[2]

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1204 Calvo-Rio 2017 [1]	Multicenter retrospective observational study	1 year	25 patients with JIA-Uveitis refractory to TNFi Mean age 18.5 y/o SD 8.3 years	Tocilizumab 8mg/kg IV every 4 weeks	Improvement in anterior chamber cell numbers 1 Month: 64% 3 Month: 68% 6 Month: 79.2% Serious adverse events: severe autoimmune thrombocytopenia in 1 patient, pneumonia and then autoimmune anemia and thrombocytopenia in 1 patient, and viral conjunctivitis and bullous impetigo in 1 patient.
1208 Tappeiner 2016 [2]	Multicenter retrospective observational study	1 year	17 patients with JIA-uveitis refractory to TNFi Mean age 15.3 y/o SD 6.9 years	Tocilizumab 8mg/kg IV every 4 weeks	Following TCZ treatment (mean followup time 8.5 mos, range 3–12 months), uveitis inactivity was achieved in 4 out of 17 patients (23.5%) at 3 months, in 5 out of 14 patients (35.7%) at 6 months, in 5 out of 9 patients (55.6%) at 9 months, and in 4 out of 8 patients (50.0%) at 12 months. In 5 patients, TCZ was discontinued (2 patients after 3 mos and 3 patients after 6 mos) because of the lack of efficacy. New ocular complications were observed in 4 patients during the TCZ treatment (cataract, n = 2; band keratopathy, n = 1; posterior synechia, n = 1; ocular hypertension, n = 1; glaucoma, n = 1)

References

1. Calvo-Rio V, Santos-Gomez M, Calvo I, Gonzalez-Fernandez MI, Lopez-Montesinos B, Mesquida M, et al. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. Arthritis Rheumatol. 2017;69(3):668-675.
2. Tappeiner C, Mesquida M, Adan A, Anton J, Ramanan AV, Carreno E, et al. Evidence for Tocilizumab as a Treatment Option in Refractory Uveitis Associated with Juvenile Idiopathic Arthritis. J Rheumatol. 2016;43(12):2183-2188.

PICO 25. In children and adolescents with JIA with active CAU, who have failed TNFi (one or more), should rituximab versus any other medication be recommended?

Summary: This PICO was addressed using one very small retrospective case series (n=8) that showed that rituximab treatment lead to uveitis inactivity in all 8 patients.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1296, Miserocchi E, 2015	Retrospective observational study (case series)	Mean ± SD follow-up time on rituximab was 44.75 ± 4.9 months	8 patients with severe longstanding JIA uveitis despite treatment with TNFi (ANA positive, and negative for RF and HLA-B27 antigen) Age: mean 22.8 ± 5.5 years Mean age at onset of uveitis was 4.7 ± 3.6 year Mean ocular disease duration: 17.7 years	Rituximab 1000mg at day 1 and 15 and then every 6 months Mean # of infusions 8.75 (range 6-12)	All 8 patients achieved complete control of uveitis and at last follow up presented with inactive uveitis. Mean ± SD uveitis activity before treatment was 2.7 ± 0.4 cells and 0.4 ± 0.3 cells at last follow-up 6/8 patients had one recurrence of uveitis 2 of those patients having two recurrences during the study.

References

1. Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol 2016;100:782-786.

PICO 26. In children and adolescents with JIA with active CAU but no active arthritis, should mycophenolate versus any other medication be recommended?

Summary: This PICO was addressed using one retrospective case series which showed a limited response (36%) to mycophenolate mofetil in JIA patients who failed or did not tolerate MTX.

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1704, Sobrin L, 2008	Retrospective case series	January 1, 1998 and June 30, 2006 Patients were seen every 6 weeks for an ocular examination	Eighty-five patients with scleritis and/or uveitis who failed with or did not tolerate methotrexate and were subsequently treated with mycophenolate mofetil between 1998 and 2006 **25 patients had JIA**	Mean duration of mycophenolate mofetil therapy was 15 months (range, 1–66). Patients with treatment durations of <6 months consisted solely of those who had to discontinue mycophenolate mofetil because of an adverse event. Average maximal daily dose administered was 1.9 g (range, 0.5–3).	9/25 (36%) of the JIA patients achieved control of the uveitis

References

1. Sobrin L, Christen W, Foster S. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmol 2008;115:1416-1421.

PICO 27. In children and adolescents with JIA with active CAU but no active arthritis, should leflunomide versus any other medication be recommended?

Summary: This PICO was addressed using one retrospective comparative study which showed no significant difference in benefit of leflunomide over MTX in the recurrence of uveitis flares in children with JIA associated uveitis.[1] An additional retrospective case series of 13 children with JIA-associated CAU found that 8/13 (61.5%) responded to LFN treatment (the study did not have a comparison group of patients receiving MTX).[2]

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1322, Bichler, 2015	Single-center retrospective cohort study	January 2010 – October 2011	15 JIA children initially received MTX and were then switched to leflunomide Ten patients showed uveitis prior to treatment, while five patients developed uveitis on treatment with MTX.	The median duration of MTX therapy was 51 (range 26–167) months; LFN was given for a median of 12 (range 4–47) months. Anti-tumour necrosis factor (anti-TNF-α) co-medication was given to four children while on MTX. By contrast, LFN was combined with anti-TNF-α treatment in 6 children.	Within a total of 1012 months of MTX treatment, 25 anterior uveitis flares occurred, compared to 16 flares within 265 months of LFN treatment. This corresponds to a mean anterior uveitis flare rate of 0.0247 flares/month on MTX and 0.0605 flares/month on LFN treatment. Subtracting treatment time on MTX or LFN and a concurrent monoclonal anti-TNF antibody, patients had 969 months of MTX treatment with 25 anterior uveitis flares, and 190 months of LFN treatment with 11 flares, corresponding to a mean anterior uveitis flare rate of 0.0259 flares/month on MTX and 0.0579 flares/month on LFN treatment
1448, Molina 2013[2]	Single-center retrospective case series	Mean follow-up 33.69 months	13 JIA patients with CAU received LEF	Mean duration of LFN therapy was 33.69 months (range 7-76 months)	8/13 patients (61.5%) responded to LFN. 4/8 responders (50%) achieved and maintained complete inactivity during follow-up, 2/8 (25%) achieved moderate improvement, and 2/8 (25%) had persistence of already quiescent inflammatory ocular disease. Responders had 17 severe complications (in 8

					patients), while the 5 non-responders had 7 severe complications. These complications were considered related to uveitis, not LFN treatment. LFN was discontinued in 1 patient due to mild GI side effects.

References

1. Bichler J, Benseler SM, Krumrey-Langkammerer M, Haas J-P, Hugle B. Leflunomide is associated with a higher flare rate compared to methotrexate in the treatment of chronic uveitis in juvenile idiopathic arthritis. Scand J Rheumatol 2015;44:280-283.
2. Molina C, Modesto C, Martin-Begue N, Arnal C. Leflunomide, a valid and safe drug for the treatment of chronic anterior uveitis associated with juvenile idiopathic arthritis. Clin Rheumatol 2013; 32:1673-1675.

PICO 28: In children and adolescents with JIA with active CAU but no active arthritis, what are the benefits and harms of cyclosporine compared to any other medication?

Summary. Two retrospective cohort studies addressed this question. One study showed that cyclosporine (CsA) was associated with a significantly lower rate of achieving inflammation control compared to other drugs.[1] The other study did not compare CsA monotherapy to other drugs, it only compared CsA monotherapy to combination therapy with CsA plus MTX and/or other systemic immunosuppressives, and found CsA monotherapy to be less effective at achieving uveitis inactivity compared to combination therapy.[2] The results appear in the table below.

Overall quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1256, Kolomeyer A., 2016 [1]	Retrospective cohort study	5 years	82 patients (74% anterior uveitis), 243 treatment regimens	Cyclosporine (CsA), methotrexate, TNF alpha inhibitors, other biologic agents	Compared to other drugs, CsA had a lower rate of achieving inflammation control (6.7% vs 33%; p = 0.09) After statistical adjustment for other variables possibly affecting inflammation control (age at disease diagnosis, type of uveitis, duration of treatment regimens, and baseline visual acuity), CSA showed a significantly lower likelihood of achieving inflammation control compared to other drug classes (OR 0.26, 95% CI 0.079-0.86).
1690, Tappeiner 2009[2]	Retrospective cohort study	Mean 3.9 years of CsA (range 1-12 years)	82 children with JIA-associated CAU	CsA monotherapy in 21 patients, the remaining patients received CsA plus 1 or more systemic therapies (MTX, azathioprine, prednisone, adalimumab, etanercept, and LFN). MTX was the most common additional agent (used in 45 patients)	CsA monotherapy: 6/25 patients (24%) achieved uveitis inactivity. CsA combined with other immunosuppresives: 35/72 patients (48.6%) achieved inactivity. (p-value compared to monotherapy = 0.037). CsA combined with MTX: 18/37 (48.6%) achieved inactivity (p-value compared to monotherapy = 0.065). CsA allowed reduction of steroids and systemic immunosuppressives by ≥50% in 19 patients. CsA allowed topical steroid reduction to ≤2 drops/eye/day in 40 patients. CsA was discontinued due to adverse effects in 9 patients.

References:

1. Kolomeyer A. et al. Chronic Non-infectious Uveitis in Patients with Juvenile Idiopathic Arthritis. 2016. Ocular Immunology and Inflammation, 24:4, 377-385, DOI: 10.3109/09273948.2015.1125509
2. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye 2009;23:1192-1198.

PICO 29: For children and adolescents with uveitis that is well controlled on systemic therapy only, when should therapy be weaned?

Summary: The literature searches identified three retrospective studies that addressed this question. In one study[1] with 59 patients on treatment with adalimumab, 20 patients discontinued treatment, 2 (10%) patients after the 1st year, 9 (45%) after the 2nd year, and 9 (45%) later than 2 years, with different reasons for discontinuation such as reactivation of uveitis (n = 8) or arthritis (n = 4), or ≥2 years of complete disease inactivity (n=3). In another study [2], 68% of patients discontinued treatment after 1 year, 36% of patients discontinued after 2 years. Likelihood of uveitis reactivation was significantly higher among patients who discontinued TNFi (see detailed results in table below). In the third study, relapse-free survival after the withdrawal of MTX was significantly longer in patients who had been treated with MTX longer than 3 years, children who were older than 8 years at the time of withdrawal, and patients who had an inactivity of longer than 2 years before the withdrawal of MTX [3].

Overall Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1205, Breitbach M., 2016 [1]	Retrospective study	2 years	68 JIAU patients	Adalimumab	59 of 68 patients who were treated with ADA achieved a sufficient response to treatment within 6 months. 39 patients (66.1 %) were still on therapy at their last follow-up visit (mean treatment duration 38.3 months, range 12–91). In another 20 patients, ADA had been discontinued after 1 or 2 years or later, in 10 % (n = 2), 45 % (n = 9) and 45 % (n = 9) of patients, respectively (mean 30.6 months; range 10–65). Reasons for discontinuing ADA were reactivation of uveitis (n = 8, 3.93 per 100 patient-years) or arthritis (n = 4; 1.97 per 100 patient-years), or ≥2 years of complete disease inactivity (n = 3, 1.47 per 100 patient-years), adverse events (n = 4; 1.89 per 100 patient-years), or other (n = 1; 0.47 per 100 patient-years).
1331, Lerman M., 2015 [2]	Retrospective case series	12 months	50 patients with risk of development of uveitis under TNFi treatment	anti-TNFα. The probability of a uveitis reactivation was estimated at 3, 6, 9 and 12 months	Of patients who discontinued anti-TNFα, two-thirds (68.4%) were on anti-TNFα for more than 1 year after achieving quiescence, but only one third were on anti-TNFα for more than 2 years after achieving quiescence (36.8%). The median time on anti-TNFα from achievement of quiescence to discontinuation was 1.73 years (IQR: 0.25-2.15). The likelihood of uveitis reactivation was higher after anti-TNFα discontinuation (63.8%) than before (24.4%). Estimated probability of uveitis reactivation was 17.9% by 3 months, 38% by 6 months, and 54.8% by 9 months in patients who discontinued TNFi. Among those

					patients, likelihood of failure was significantly higher for those treated with adalimumab vs. infliximab (hazard ratio 13.4, 95% CI 2.2-82.5).
1588, Ayuso V., 2011	Retrospective case series	9 months	22 JIA patients treated with MTX for active uveitis	MTX	Longer inactivity under MTX therapy was independently protective for relapses after the withdrawal (hazard ratio = 0.07; 95% confidence interval 0.01-0.86; P = .038), which means that 1-year increase of duration of inactive uveitis before the withdrawal of MTX results in a decrease of hazard for new relapse of 93%. Relapse-free survival after the withdrawal of MTX was significantly longer in patients who had been treated with MTX longer than 3 years, children who were older than 8 years at the moment of the withdrawal, and patients who had an inactivity of longer than 2 years before the withdrawal of MTX.

References:

1. Breitbach M., Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis, Graefes Arch Clin Exp Ophthalmol (2017) 255:171–177. DOI 10.1007/s00417-016-3497-5
2. Lehman M., Uveitis Reactivation in Children Treated with Tumor Necrosis Factor-α Inhibitors. Am J Ophthalmol. 2015 July; 160(1): 193–200.e1. doi:10.1016/j.ajo.2015.04.016.
3. Ayuso KV, van de Winkel EL, Rothova A, & de Boer JH. Relapse Rate of Uveitis Post-Methotrexate Treatment in Juvenile Idiopathic Arthritis. American Journal of Ophthalmology 2011; 151(2): 217-222. doi:10.1016/j.ajo.2010.08.021

PICO 30. For children and adolescents with spondyloarthritis starting a TNFi for arthritis, does etanercept versus any other TNFi influence the risk of developing AAU or recurrent AAU?

Summary: The literature searches did not identify any pediatric studies that addressed this PICO question. The table below provides a summary of data taken from PICO 29 in the 2015 ACR/SAA/SPARTAN guideline Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. The studies in table 2 enrolled primarily adult patients with spondyloarthropathies, so they provide only indirect evidence for PICO 33. The evidence report states the following: "This PICO was not directly addressed by any head-to-head RCTs. Four observational studies or pooled analyses of RCTs compared rates of iritis between patients treated with etanercept and either infliximab (4 studies) or adalimumab (2 studies). All studies reported higher rates among patients treated with etanercept than with infliximab/adalimumab, with relative risks of 8.6, 2.3, 22.7, and infinity."

Quality of evidence across all critical outcomes: Very low

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall quality of evidence	No. of patients		Relative effect (95% CI)	Anticipated absolute effects	
							Control: Etanercept	TNFi monoclonals		Risk with etanercept	Risk difference with TNFi monoclonals
Iritis flare Rate/100 Patient-Years (follow-up 2-16 years; Better indicated by lower values)											
4 observational studies [a]	serious	not serious	not serious	serious[b]	strong association[c]	⨁OOO VERY LOW	113[d]	339[e]	-	-	mean 28.7 lower (unable to calculate CI)[f]

Explanations

a. 3 cohort studies and study of 1 pooled data from RCTs

b. Unclear how flare was defined and rates varies substantially between cohort studies

c. Substantial and consistently greater flares for etanercept across all 4 studies

d. Etanercept

e. Either infliximab or adalimumab (only 15 total on adalimumab)

f. Mean rate in etanercept 31.9 flares/100PY; mean rate for monoclonals: 3.2 flares/100PY

References

1. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis 2006;65:1631-4.
2. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 2005;52:2447-51.
3. Cobo-Ibanez T, del Carmen OM, Munoz-Fernandez S, Madero-Prado R, Martin-Mola E. Do TNF-blockers reduce or induce uveitis? Rheumatology (Oxford) 2008;47:731-2.
4. Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Bacquet-Deschryver H, Kozyreff-Meurice M, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology (Oxford) 2009;48:761-4.

PICO 31. For children and adolescents with spondyloarthritis starting a TNFi for arthritis, does the choice of TNFi influence the risk of developing AAU or recurrent AAU?

Summary: The literature searches did not identify any pediatric studies that addressed this PICO question. The table below provides a summary of data taken from PICO 29 in the 2015 ACR/SAA/SPARTAN guideline Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. The studies in table 2 enrolled primarily adult patients with spondyloarthropathies, so they provide only indirect evidence for PICO 33. The evidence report states the following: "This PICO was not directly addressed by any head-to-head RCTs. Four observational studies or pooled analyses of RCTs compared rates of iritis between patients treated with etanercept and either infliximab (4 studies) or adalimumab (2 studies). All studies reported higher rates among patients treated with etanercept than with infliximab/adalimumab, with relative risks of 8.6, 2.3, 22.7, and infinity."

Quality of evidence across all critical outcomes: Very low

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall quality of evidence	No. of patients		Relative effect (95% CI)	Anticipated absolute effects	
							Control: Etanercept	TNFi monoclonals		Risk with etanercept	Risk difference with TNFi monoclonals
Iritis flare Rate/100 Patient-Years (follow-up 2-16 years; Better indicated by lower values)											
4 observational studies [a]	serious	not serious	not serious	serious[b]	strong association[c]	⨁OOO VERY LOW	113[d]	339[e]	-	-	mean 28.7 lower (unable to calculate CI)[f]

Explanations

a. 3 cohort studies and study of 1 pooled data from RCTs

b. Unclear how flare was defined and rates varies substantially between cohort studies

c. Substantial and consistently greater flares for etanercept across all 4 studies

d. Etanercept

e. Either infliximab or adalimumab (only 15 total on adalimumab)

f. Mean rate in etanercept 31.9 flares/100PY; mean rate for monoclonals: 3.2 flares/100PY

References

1. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis 2006;65:1631-4.
2. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 2005;52:2447-51.
3. Cobo-Ibanez T, del Carmen OM, Munoz-Fernandez S, Madero-Prado R, Martin-Mola E. Do TNF-blockers reduce or induce uveitis? Rheumatology (Oxford) 2008;47:731-2.
4. Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Bacquet-Deschryver H, Kozyreff-Meurice M, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology (Oxford) 2009;48:761-4.

PICO 32. In children and adolescents with spondyloarthritis, is education regarding the warning signs of AAU more effective versus no education in decreasing delay in treatment, duration of symptoms, or complications of iritis?

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

Quality of evidence across all critical outcomes: Very low

PICO 33. In children and adolescents with spondyloarthritis, are TNFi monoclonal antibodies more effective in decreasing the occurrence or rate of recurrence of episodes of iritis versus etanercept?

Summary: The literature searches did not identify any pediatric studies that addressed this PICO question. The table below provides a summary of data taken from PICO 29 in the 2015 ACR/SAA/SPARTAN guideline Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. The studies in table 2 enrolled primarily adult patients with spondyloarthropathies, so they provide only indirect evidence for PICO 33. The evidence report states the following: “This PICO was not directly addressed by any head-to-head RCTs. Four observational studies or pooled analyses of RCTs compared rates of iritis between patients treated with etanercept and either infliximab (4 studies) or adalimumab (2 studies). All studies reported higher rates among patients treated with etanercept than with infliximab/adalimumab, with relative risks of 8.6, 2.3, 22.7, and infinity.”

Quality of evidence across all critical outcomes: Very low

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall quality of evidence	No. of patients		Relative effect (95% CI)	Anticipated absolute effects	
							Control: Etanercept	TNFi monoclonals		Risk with etanercept	Risk difference with TNFi monoclonals
Iritis flare Rate/100 Patient-Years (follow-up 2-16 years; Better indicated by lower values)											
4 observational studies [a]	serious	not serious	not serious	serious[b]	strong association[c]	⨁OOO VERY LOW	113[d]	339[e]	-	-	mean 28.7 lower (unable to calculate CI)[f]

Explanations

a. 3 cohort studies and study of 1 pooled data from RCTs

b. Unclear how flare was defined and rates varies substantially between cohort studies

c. Substantial and consistently greater flares for etanercept across all 4 studies

d. Etanercept

e. Either infliximab or adalimumab (only 15 total on adalimumab)

f. Mean rate in etanercept 31.9 flares/100PY; mean rate for monoclonals: 3.2 flares/100PY

References

1. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis 2006;65:1631-4.
2. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 2005;52:2447-51.
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4. Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Bacquet-Deschryver H, Kozyreff-Meurice M, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology (Oxford) 2009;48:761-4.

PICO 34. In children and adolescents with spondyloarthritis who develop iritis while treated with a TNFi, is switching the TNFi more effective in decreasing recurrences of iritis versus continuing the same TNFi?

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

Quality of evidence across all critical outcomes: Very low

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Ayuso KV, van de Winkel EL, Rothova A, & de Boer JH. Relapse Rate of Uveitis Post-Methotrexate Treatment in Juvenile Idiopathic Arthritis. American Journal of Ophthalmology 2011; 151(2): 217-222.

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