South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Tumor Necrosis Factor inhibitor (TNFi) therapy for the use in children & adolescents with Polyarticular Juvenile Idiopathic Arthritis (JIA) *with uveitis* (PICO 2) who are refractory to conventional disease modifying anti-rheumatic drugs (DMARDs). *Please see accompanying document for PICO 1 - *JIA without uveitis*

Date: March 2023

Key findings

- This document reports on the findings for PICO 2 – Juvenile Idiopathic Arthritis (JIA) with JIA related uveitis. Evidence related to PICO 1, as well as overall costing and recommendation for both PICOs are presented in the accompanying document.
- For PICO 2, we identified 1 systematic review and 3 guidelines for inclusion. The systematic review was assessed with the AMSTAR 2 tool and evaluated to be of moderate quality.
- ***PICO 2 – patients with polyarticular JIA with uveitis – (1 systematic review of 3 RCTs, n = 134)***

  The systematic review reported results from two analyses; one set a priori and another post-hoc. A post-hoc analysis was conducted as the a priori definition for the primary outcomes was found to be quite narrow resulting in exclusion of most trials and/or participants. We report on both below.

  TNF inhibitors versus placebo

  - Number of participants with treatment success/response (as defined by the individual study)
    TNF inhibitors may improve treatment success (as per the above definition) compared to placebo (RR=2.60, 95% CI [1.30 to 5.20], P = 0.007 - significant, i^2=0%) – 3 RCTs, n=124, low quality. **Summary of Findings table – Comments section**. At a subgroup level, adalimumab was superior to placebo and no difference was found between etanercept and placebo.
  - Number of participants with treatment failure (as defined by the individual study)
    TNF inhibitors may reduce treatment failure (as per the above definition) compared to placebo (RR=0.23, 95% CI [0.11 to 0.50], P = 0.0002 - significant, i^2=0%) – 3 RCTs, n=133, low quality. **See Summary of Findings table – Comment section**. At a subgroup level, adalimumab was superior to placebo and etanercept was superior to placebo however the result for etanercept was not statistically significant.
  - No. participants with treatment success defined as 0 to trace cells; or 2-step decrease in SUN AC cell grading
    TNF inhibitors may improve treatment success (as per the above definition) compared to placebo (RR=0.66, 95% CI [0.21 to 2.10], I^2=0%, P = 0.49 – not significant) – 2 RCT, n=43, Low certainty. **See Summary of Findings table.**
  - No. participants with treatment failure defined as 2-step increase in SUN AC cell grading
    TNF inhibitors may reduce treatment failure (as per the above definition) compared to placebo (RR=0.31, 95% CI [0.01 to 7.15], P = 0.47 – not significant) – 1 RCT, n=31, Low certainty. **See Summary of Findings table.**
  - Safety
    No serious adverse events were reported in the etanercept trial or the ADJUVITE adalimumab trial. Rate of serious events were higher in the adalimumab group in the SYCAMORE trial compared to placebo. Rates per person-year of injection site reactions, respiratory disorders and gastrointestinal disorders were higher in the adalimumab groups compared to the placebo groups
- A high-quality clinical practice guideline (AGREE II score of 84% overall and 83% for rigour) by American College of Rheumatology and the Arthritis Foundation (2019) conditionally recommends starting methotrexate and a TNF inhibitor immediately over methotrexate as monotherapy if individuals have severe active chronic anterior uveitis and sight threatening complications (very low quality). Additionally the guidelines conditionally recommend adalimumab or infliximab over etanercept (very low quality).
- Costs (See accompanying PICO 1 document)

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Rationale: The Tertiary and Quaternary Hospital Level Committee suggests adalimumab for children and adolescents with Polyarticular Juvenile Idiopathic Arthritis (JIA) without JIA related uveitis (PICO 1) and with uveitis (PICO 2) who are refractory to conventional disease modifying anti-rheumatic drugs (DMARDs).
PICO 1: TNF inhibitors likely decrease JIA disease flares and may increase treatment response. The individual trials show that adalimumab and etanercept were both superior to placebo for the two outcomes.
PICO 2: TNF inhibitors may improve treatment response and reduce treatment failure for uveitis. Evidence appeared more favourable for adalimumab compared to placebo than etanercept compared to placebo.

Both adalimumab and etanercept are administered subcutaneously which is feasible in terms of administration however adalimumab is less resource intensive. Adalimumab is more resource intensive than current standard of care.

Level of Evidence: Disease flare – moderate certainty, JIA ACR Pedi 30% response – low certainty, treatment success and failure for uveitis – low to moderate certainty.

(Refer to appendix 1 for the evidence to decision framework)

Summary of findings tables

PICO 2 - JIA with uveitis (combined TNFi compared to placebo)

Summary of findings 1. Summary of findings

TNF inhibitors compared with placebo for participants with JIA-associated uveitis

Patient or population: Participants with a diagnosis of JIA and uveitis who are aged 2 to 18 years old
Settings: University hospitals and tertiary care hospitals
Intervention: TNF inhibitors (Etanercept or Adalimumab)
Comparison: Placebo

Outcomes	Illustrative comparative risks*[1] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Proportion of participants with success, defined as 0 to trace cells or 2-step decrease in activity SUN-grading (range: 0 to 4+, higher score indicates severe condition) at 2 or 6 months	250 per 1000	165 per 1000 (53 to 525)	**RR 0.66** (95%CI 0.21 to 2.10)	43 (2)	⊕⊕⊖⊖ Low[1]	*Post hoc* analysis using the individual trial definitions of treatment response shows a RR of treatment success of 2.60 (95% CI 1.30 to 5.20; 3 studies; 124 participants); the effect was in favor of adalimumab over placebo while evidence on etanercept was very limited
Risk of failure defined as 2-step increase in activity in SUN grading (range: 0 to 4+, higher score indicates severe condition) at 2 or 6 months	67 per 1000	21 per 1000 (1 to 477)	**RR 0.31** (95%CI 0.01 to 7.15)	31 (1)	⊕⊕⊖⊖ Low[1]	*Post hoc* analysis using the individual trial definitions of treatment failure of 0.23 (95% CI 0.11 to 0.50; 3 studies; 133 participants); the effect was in favor of adalimumab over placebo while evidence on etanercept was very limited
Systemic complication	See comments.		-	122 (2)		Injection site reaction (rate ratio 9.88; 95% CI 4.69 to 20.78) and gastrointestinal disorders (rate ratio 4.78; 95% CI 2.72 to 8.38)

*[1]The **assumed risk** is based on the estimate in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

*[2]The estimates is based on the analyses presented in the included study.
CI: confidence interval; **JIA**: juvenile idiopathic arthritis; **logMAR:** logarithm of the minimum angle of resolution; **RR:** risk ratio; **SUN:** standardization of uveitis nomenclature; **TNF**: tumor necrosis factor

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]Downgraded two levels for imprecision due to wide confidence intervals.
[2]Downgraded one level for indirectness of evidence.

BACKGROUND

*Please see accompanying document for background on JIA.

Acute or chronic uveitis is an extra-articular manifestation found in some individuals with JIA. Persistent or recurrent uveitis can result in complications such cataracts, synechiae, glaucoma and band keratopathy, which may lead to blindness in up to 10% of children[1].

RESEARCH QUESTION

Is it safe and effective to add a tumor necrosis factor inhibitor (TNFi) to conventional synthetic DMARDs in patients with JIA *with uveitis* having an inadequate response or being intolerant to NSAIDs, intra-articular glucocorticoids, and methotrexate?

Due to the outcomes assessed in trials differing for individuals with uveitis, evidence for the specific group was evaluated to determine if evidence aligned with PICO 1 (without uveitis) in terms of superiority of individual TNF inhibitor agents as well as pooled efficacy of TNF inhibitors compared to placebo.

Eligibility criteria for review

PICO 2: Tumor necrosis factor inhibitors for individuals with JIA **with** uveitis	
Population	Children, Adolescents & young adults with Juvenile Idiopathic Arthritis **with** uveitis refractory or intolerant to NSAIDs, intra-articular glucocorticoids and methotrexate.
Intervention	• Addition of a TNF-i to current standard of care • TNFi: Adalimumab, Etanercept, Golimumab, Infliximab
Comparator/s	• Current standard of care (NSAIDS, intra-articular glucocorticoids, methotrexate) AND / OR • Placebo
Outcome/s	Primary Outcomes: - Number with a treatment/success response as per individual study classification - Number with flare/treatment failure as per individual study classification Secondary Outcomes: - Treatment success defined as 0 to trace cells; or 2-step decrease in activity using in SUN anterior chamber (AC) cell grading - Treatment failure defined as 2-step increase in SUN anterior chamber (AC) cell grading - Adverse events
Study design/s	Randomized Controlled Trials/systematic reviews/meta-analyses International Treatment Guidelines.

METHODS

A rapid search of evidence was conducted in PubMed and the Cochrane Library in November 2022 for both PICOs (See accompanying document for PICO 1). Studies included with the submitted motivation were also assessed for inclusion. Screening and selection of articles were conducted independently by two reviewers (JR and KM). Data extraction was conducted by two reviewers (JR and KM) and reviewed by the ERC. An AMSTAR 2[2] assessment was conducted independently and in duplicate on the selected systematic review (KM and JR).

RESULTS

Results of the search

The search produced 353 results (both PICO 1 and 2) and sixteen duplicates were removed. After title and abstract screening, full text review was carried out on 43 articles (18 trials, 16 SRs or MAs, 9 guidelines – both PICO 1 and 2). For PICO 2 one systematic review and 3 guidelines were included for data extraction (See Appendix 1 – Characteristics of included studies and Table 1 under the Guidelines section). See accompanying document on PICO 1 for a summary of the excluded studies (PICO 1 and 2) as well as PRISMA diagram.

Description of studies included

PICO 2 – Tumor necrosis factor inhibitors for individuals with JIA **with uveitis**

- A Cochrane systematic review conducted by Renton *et al.* (2022)[3] aimed to evaluate the effectiveness and safety of TNF inhibitors used for treatment of JIA associated uveitis in individuals aged 2 to 18 years old (3 RCTS[4,5,6], n=134). The review explored the difference between TNF inhibitors (adalimumab, etanercept, infliximab, golimumab or certolizumab) without or with other agents (provided both groups received) and placebo. The primary outcome of the review was defined as treatment success or failure at two to six months based on Standardization of Uveitis Nomenclature (SUN) Criteria score for anterior chamber (AC) cell grading and adverse events. The review reported difficulties in assessing based on these criteria as trials categorised success and failure on a combination of measurements thus post-host analyses were performed exploring treatment success and failure as defined by the included RCTs. Results of both will be presented below.

Risk of bias

The systematic review conducted risk of bias 2 assessment on the three included RCTs for the primary outcomes. Outcomes for the three studies across all domains were rated as 'low risk' except for the domain related to bias in measurement of the outcome for the adalimumab study[6]. The outcomes were judged to have 'some concerns' as it was unclear whether assessors were masked to the treatment assignments.

Effects of Interventions

PICO 2 – Tumor necrosis factor inhibitors for individuals with JIA **with uveitis** (1 Cochrane SR)[3]

Efficacy

Comparison 1: TNF inhibitors versus placebo (3 RCTs, n=134)

Outcome 1.1: Treatment success/response as defined by the individual study:

More participants had treatment success as per the RCT's definition thereof in the TNF inhibitor (n=32, 41.6%) group compared to the placebo (n=8, 17%) group (RR=2.60, 95% CI [1.30 to 5.20], NNT=4 95% CI [3 to 13]; P = 0.007 - significant, i^2=0%) – *3 RCTs, n=124 (moderate quality).* See Figure 1 below. At a subgroup level, more participants had treatment success in the adalimumab (n=29, 41.4%) group compared to the placebo (n=6, 14.3%) group (RR=3.11, 95% CI [1.40 to 6.90], NNT = 4; P = 0.005 - significant, i^2=0%) – *2 RCTs, n=112*. Number of participants with treatment success was similar between the etanercept and placebo groups (RR=1.07, 95% CI [0.27 to 4.23]; P = 0.92 – not significant) – *1 RCTs, n=12*.

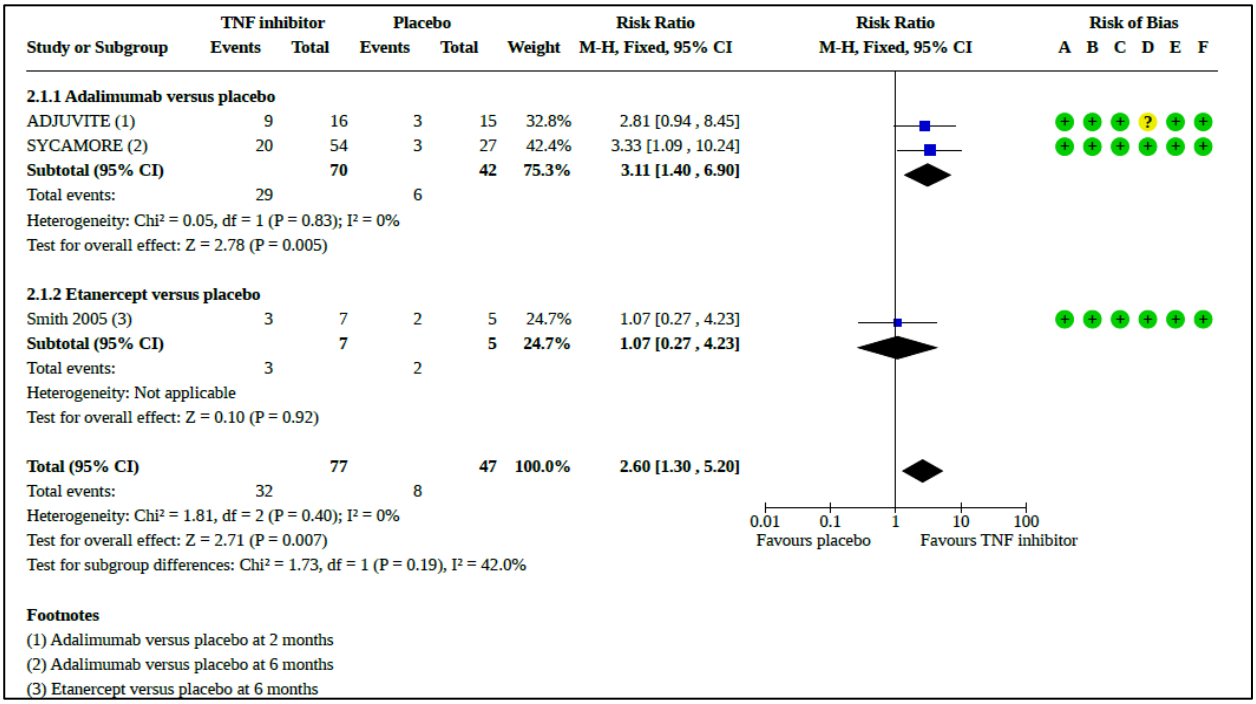

Figure 1: Forest Plot – Outcome 1.1 Treatment response as defined by the individual study

Outcome 1.2: Treatment failure as defined by the individual study

TNF-inhibitors may reduce treatment failure (low certainty). Less participants had treatment failure as per the RCT's definition thereof in the TNF inhibitor (n=7, 8.4%) group compared to the placebo (n=17, 34%) group (RR=0.23, 95% CI [0.11 to 0.50], P = 0.0002 - significant, i^2=0%) – *3 RCTs, n=133 (moderate quality).* See Figure 2 below.

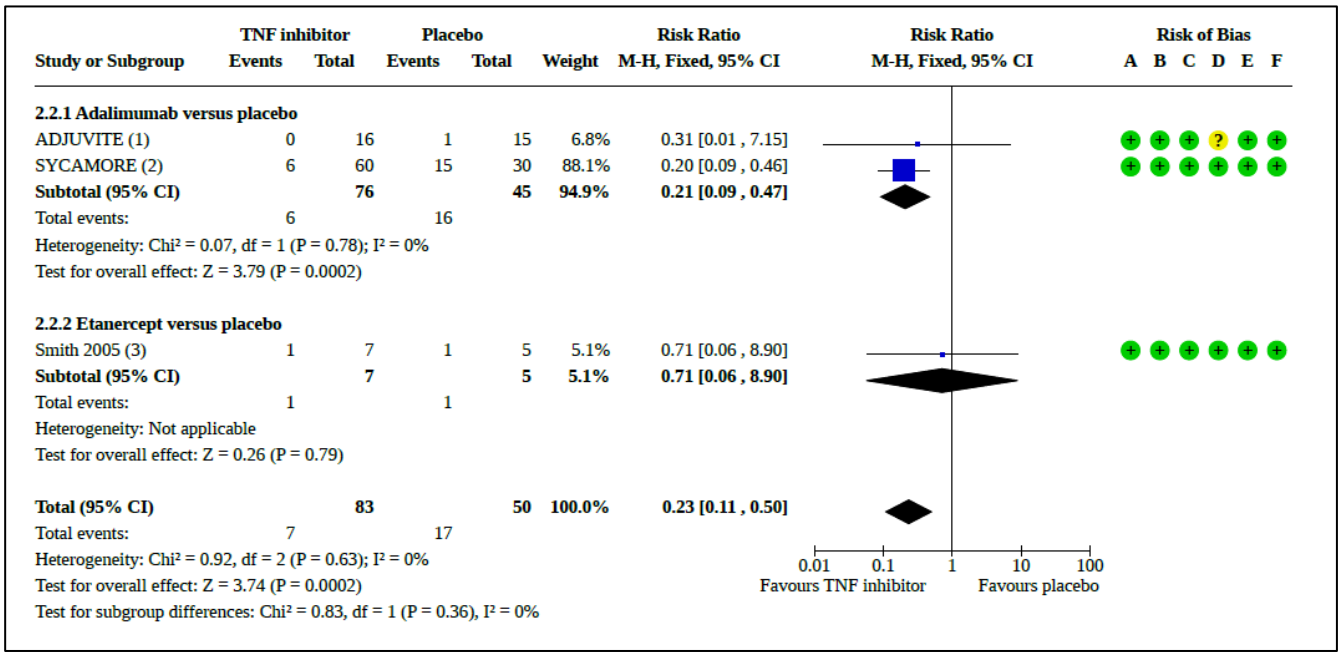

Figure 2: Forest Plot – Outcome 1.2 Treatment failure as defined by the individual study

At a subgroup level, less participants had treatment failure in the adalimumab (n=6, 7.9%) group compared to the placebo (n=16, 35.6%) group (RR=0.21, 95% CI [0.09 to 0.47], NNT= 4; P = 0.0002 - significant, i^2=0%) – 2 RCTs,

n=121. Number of participants with treatment failure was similar between the etanercept and placebo groups (RR=0.71, 95% CI [0.06 to 8.90]; P = 0.79 – not significant) – 1 RCTs, n=12.

Outcome 1.3: Treatment success defined as 0 to trace cells; or 2-step decrease in activity using in SUN anterior chamber (AC) cell grading:
The systematic review reported that less participants had treatment success as per this definition in the TNF inhibitors (n=4, 17.4%) group compared to the placebo (n=5, 25%) group (RR=0.66, 95% CI [0.21 to 2.10], I^2=0% (low heterogeneity), P = 0.49 – not significant) – *2 RCT, n=43, Low certainty of evidence.* See Figure 3 below. At a subgroup level, less participants had treatment success in the adalimumab (n=2, 12.5%) group compared to the placebo (n=3, 20%) group (RR=0.63, 95% CI [0.12 to 3.24], P = 0.58 – not significant) – *1 RCT, n=31.* A smaller percentage of participants had treatment success as per the definition in the etanercept (n=2, 28.6%) compared to the placebo (n=2, 40%) group (RR=0.71, 95% CI [0.15 to 3.50], P = 0.68 – not significant) – *1 RCT, n=12.*

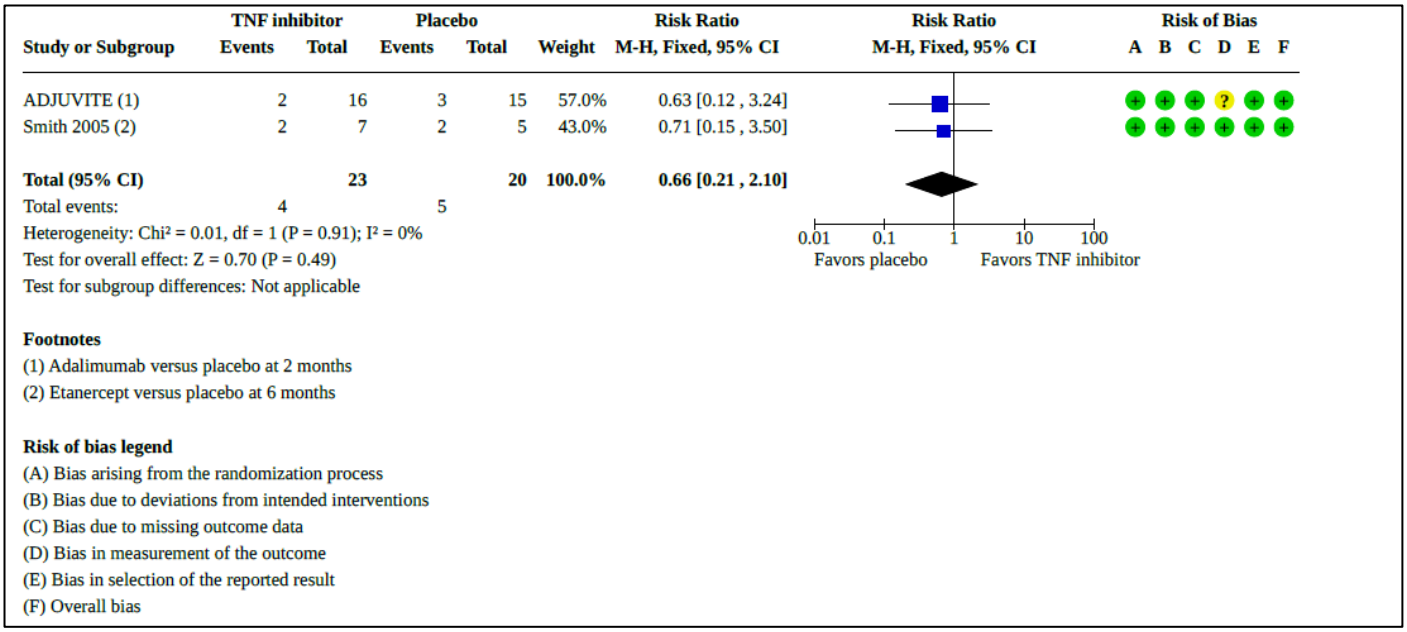

Figure 3: Forest Plot – Outcome 1.3 success defined as 0 to trace cells; or 2-step decrease in activity using in SUN anterior chamber (AC) cell grading

Outcome 1.4: Treatment failure defined as 2-step increase in SUN anterior chamber (AC) cell grading: The systematic review reported that less participants had treatment failure as per the definition in the TNF inhibitor (n=0, 0%) group compared to the placebo (n=1, 6.7%) group (RR=0.31, 95% CI [0.01 to 7.15], P = 0.47 – not significant) – *1 RCT, n=31, Low certainty of evidence.* See Figure 4 below. Outcome only included one trial (adalimumab).

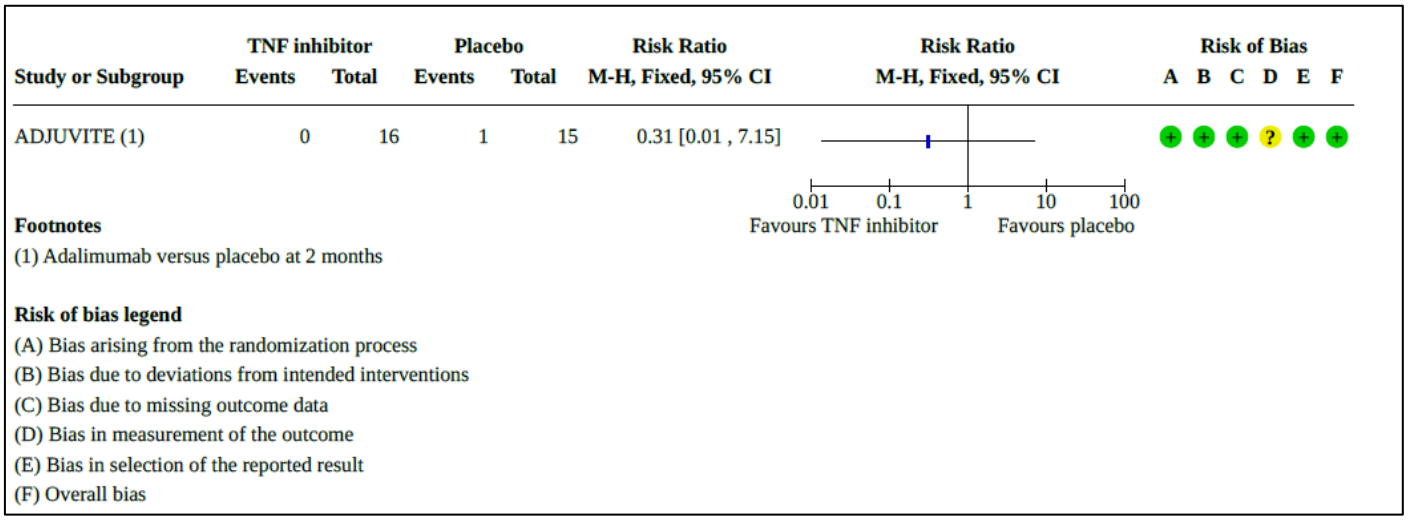

Figure 4: Forest plot – Outcome 1.4 Treatment failure defined as 2-step increase in SUN anterior chamber (AC) cell grading

Outcome 1.5: Serious adverse events

No serious adverse events related to treatment were reported in the ADJUVITE trial (adalimumab)[6]. The rate of serious adverse events in the SYCAMORE trial[5] was higher in the adalimumab group compared to the placebo group at 0.29 events per patient-year (95% CI 0.15 to 0.43) and 0.19 events per patient-year (95% CI 0.00 to 0.40), respectively. No serious adverse events were reported in the Smith *et al*. trial[4].

Outcome 1.6: Systemic adverse events

- Only trials for adalimumab were included for this outcome. Systematic adverse events only reported in the adalimumab studies. The systematic review reported that rate per person-year of injection site reactions was higher in the adalimumab groups compared to the placebo groups (Rate ratio=9.88, 95% CI [4.69 to 20.78], P < 0.00001 - significant, i^2=67% - moderate heterogeneity) – *2 RCTs, n=112*– See Figure 5 below.
- Systematic adverse events only reported in the adalimumab studies. The systematic review reported that rate per person-year of gastrointestinal disorders was higher in the adalimumab groups compared to the placebo groups (Rate ratio=4.78, 95% CI [2.72 to 8.38], P < 0.00001 - significant, i^2=50% - moderate heterogeneity) – *2 RCTs, n=112*– See Figure 5.
- Systematic adverse events only reported in the adalimumab studies. The systematic review reported that rate per person-year of respiratory disorders was higher in the adalimumab groups compared to the placebo groups (Rate ratio=11.43, 95% CI [5.28 to 24.74], P < 0.00001 – significant) – *1 RCT, n=70*– See Figure 5.

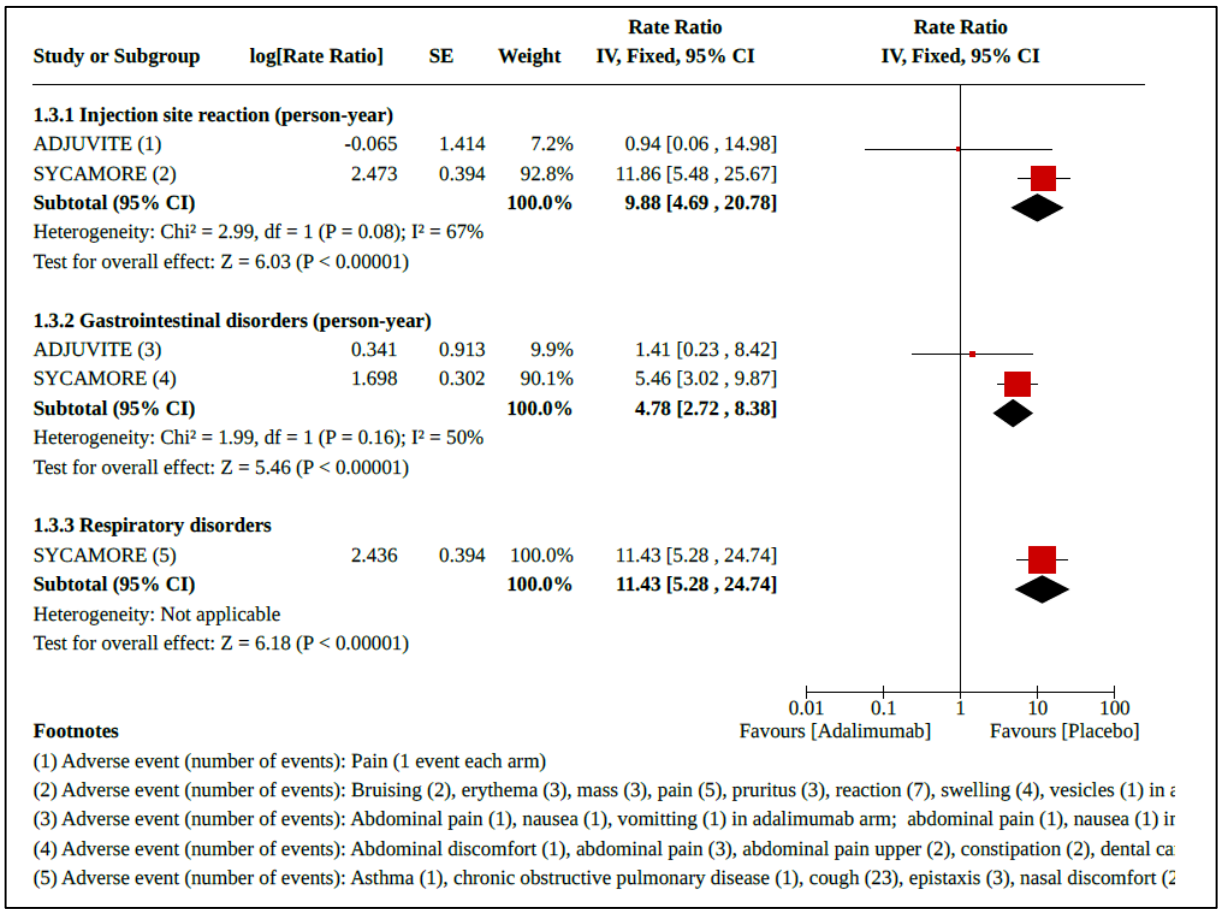

Figure 5: Forest plot – Outcome 1.6 Systematic adverse events

Quality of the Evidence

AMSTAR II was used to assess the quality of the included systematic review conducted by Renton *et al.*[3] (Appendix 2) and the review was considered to be of moderate quality. The results of the a priori analysis (Treatment success and failure defined as by increase or decrease in SUN anterior chamber (AC) cell grading – outcomes 1.3 and 1.4) were downgraded by two levels for imprecision (See Summary of Findings Table) and overall certainty was evaluated to be low. Results were not downgraded for risk of bias. The post-host analysis result did not undergo separate GRADEing however risk of bias is likely to be similar for the outcomes (outcome 1.1 and 1.2) and since the confidence levels for each result were much narrower, we considered the evidence to be of moderate certainty.

Guidelines

There were four relevant guidelines on the treatment of JIA with uveitis. These guidelines were produced by American College of Rheumatology (ACR) in collaboration with Arthritis Foundation 2019[7], Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) 2018[8] (PICO 2) and the Portuguese Society of Ophthalmology (PSO) 2022[9], and the German Society of Pediatric and Juvenile Rheumatic Diseases (GKJR) 2022[10] (covering both PICO 1 & 2). The clinical guidelines were appraised using the AGREE II tool (see Appendix 3), and were found to vary in quality from lower quality (PSO 2022, GKJR 2022, SHARE 2018) to higher quality (ACR 2019). The relevant recommendations from each guideline and selected items from the AGREE II appraisal outcome are presented in Table 1.

Table 1. Clinical guideline quality assessments and recommendations – PICO 2: JIA with uveitis

Guideline	Recommendations	Strength of evidence	AGREE II*

American College of Rheumatology (ACR) 2019[7]	<u>Recommendations for DMARDs and biologics</u> In children and adolescents with JIA and active Chronic anterior uveitis (CAU) who are/have: - *Severe active CAU and sight-threatening complications, starting methotrexate and a monoclonal antibody TNFi immediately is conditionally recommended over methotrexate as monotherapy (Recommendation 11).* - *Starting a TNFi, starting a monoclonal antibody TNFi (adalimumab or infliximab) is conditionally recommended over etanercept (Recommendation 12).*	Very low[1] Very low[2]	**Rigour of development**: 83% **Overall score:** 84%
Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) 2018[8]	15. In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended. 16. The use of anti-TNF treatment strategies (adalimumab>infliximab>golimumab) is recommended in patients with uveitis refractory/resistant to DMARD therapy, principally methotrexate. 17. Based on the current evidence, etanercept should not be considered for JIA-associated uveitis	Level 3, descriptive study; GRADE C, 92% consensus. Level 3, descriptive study; GRADE C, 100% consensus. Level 1 1B – meta-analysis of case-control studies – GRADE A - 100% consensus.	**Rigour of development:** 61% **Overall score:** 57%
German Society of Pediatric and Juvenile Rheumatic Diseases (GKJR)[10]	6. We suggest using TNF-alpha inhibition in case of inadequate response or intolerance to csDMARD therapy (e.g., MTX) in non-systemic JIA and it may also be used in systemic JIA. We suggest that the choice of TNF blocker should take into account the presence of extraarticular manifestations. Adalimumab should be used in the presence of uveitis.	100% consensus by group – no quality result reported	**Rigour of development:** 60% **Overall score:** 49%
Portuguese Society of Ophthalmology[9]	<u>Key-Statement 15</u>: JIA-Uveitis children refractory to methotrexate (MTX) or with insufficient/inadequate response to MTX should be started on biological treatment with a tumour necrosis factor-inhibitor (TNF-i). *Reasons to escalate to/initiate biological treatment are as follows:* *i) uncontrolled ocular inflammation despite 3-4 months of treatment with MTX and topical steroid at up to 3 drops/day;* *ii) patients requiring systemic immunosuppression but with contraindications to anti-metabolites or unable to tolerate MTX.* Key-Statement 16: Adalimumab (ADA) should be the first choice of biologic drug in JIA-U.	Level of agreement 8.55/9 – no quality result reported Level of agreement 8.71/9 – no quality result reported	**Rigour of development:** 48% **Overall score:** 47%

[1] Recommendation based on lack of direct evidence from studies, the risk of permanent vision loss, and anticipated differences in patient values and preferences

[2] Recommendation based on benefit of using monoclonal antibody TNFi has been shown, despite paucity of direct comparisons

COSTING AND BUDGET IMPACT: See accompanying document for costs for PICO 1 and 2

CONCLUSION

Evidence for TNF inhibitors compared to placebo for individuals with JIA and uveitis who are refractory or intolerant to standard of care was aligned with evidence for individuals without uveitis. TNF inhibitors may improve treatment response and reduce treatment failure. At an individual agent level, adalimumab compared to placebo appeared to be more effective than etanercept compared to placebo. The results aligned with international guidelines (evaluated to be of good quality) which recommended TNF inhibitors (adalimumab over etanercept) but recognised the data to be of low quality. It is concluded that the evidence between the two population groups does not differ, and that adalimumab is the preferable agent due to cost. See PICO 1 accompanying document for evidence to decision framework and recommendations.

Reviewers and declaration of interests: see accompanying document.

Appendix 1: Characteristics of included studies

Table 1. PICO 2 (JIA with uveitis)

Citation	Study design	Population (n)	Treatment	Main findings	Risk of Bias (extracted from review)
Renton *et al*. 2022[3]	Cochrane Systematic Review of RCTs	Participants aged 2 to 18 years with a diagnosis of JIA associated uveitis.	Etanercept 0,4mg/kg, subcutaneous, twice weekly OR Placebo, subcutaneous, twice weekly *(1 RCT – n=14)* Adalimumab 20-30mg/kg, subcutaneous, every 2nd week OR Placebo, subcutaneous, every 2nd week *(2 RCT – n=112)*	<u>Primary Outcome: Treatment success at two to six months</u> Two analyses were conducted – one on treatment success as defined by the review protocol (0 to trace cells; or 2-step decrease in activity using in SUN anterior chamber (AC) cell grading) and another on treatment as defined in the individual RCT (A. per protocol and B. per individual study respectively). • *Etanercept* vs placebo for the per protocol analysis RR 0.71 95% CI [0.15 to 3.50] – not significant, 1 RCT, n=12). For the per individual study analysis RR 1.07 95% CI [0.27 to 4.23] – not significant, 1 RCT, n=12). • *Adalimumab* vs placebo for the per protocol analysis RR 0.63 95% CI [0.12 to 3.24] – not significant, 1 RCT, n=31). For the per individual study analysis RR 3.11 95% CI [1.40 to 6.90] – significant, 2 RCTs, n=112). **GRADE: Outcome judged as low, downgraded two levels for imprecision of results** <u>Primary Outcome: Treatment failure at two to six months</u> Two analyses were conducted as above for treatment success • *Etanercept* vs placebo for the per protocol analysis - not estimable. For the per individual study analysis RR 0.71 95% CI [0.06 to 8.90] – not significant, 1 RCT, n=12). • *Adalimumab* vs placebo for the per protocol analysis RR 0.31 95% CI [0.01 to 7.15] – not significant, 1 RCT, n=31). For the per individual study analysis RR 0.21 95% CI [0.09 to 0.47] – significant, 2 RCTs, n=121). **GRADE: Outcome judged as low, downgraded two levels for imprecision of results** <u>Adverse effects:</u> No serious adverse events related to the treatment were reported in any of the studies (adalimumab and etanercept) For adalimumab vs placebo: • Rate per person-year of injection site reactions higher in adalimumab groups compared to placebo groups (Rate ratio=9.88, 95% CI [4.69 to 20.78], P < 0.00001 - significant, i2=67%) – 2 RCTs, n=112. • Rate per person-year of gastrointestinal disorders higher in adalimumab groups compared to the placebo (Rate ratio=4.78, 95% CI [2.72 to 8.38], P < 0.00001 - significant, i2=50%) – 2 RCTs, n=112. • Rate per person-year of respiratory disorders higher in adalimumab groups compared to placebo groups (Rate ratio=11.43, 95% CI [5.28 to 24.74], P < 0.00001 – significant) – 1 RCT, n=70. **GRADE: Outcome judged as low, downgraded two levels for imprecision of results**	**<u>Bias arising from the randomization process</u>** Smith *et al*. 2005 – Low Risk of Bias SYCAMORE 2017 – Low Risk of Bias ADJUVITE 2018 – Low Risk of Bias **<u>Bias due to deviations from intended interventions</u>** Smith *et al*. 2005 – Low Risk of Bias SYCAMORE 2017 – Low Risk of Bias ADJUVITE 2018 – Low Risk of Bias **<u>Bias due to missing outcome data</u>** Smith *et al*. 2005 – Low Risk of Bias SYCAMORE 2017 – Low Risk of Bias ADJUVITE 2018 – Low Risk of Bias **<u>Bias in measurement of the outcome</u>** Smith *et al*. 2005 – Low Risk of Bias SYCAMORE 2017 – Low Risk of Bias ADJUVITE 2018 – Some concerns **<u>Bias in selection of the reported result</u>** Smith *et al*. 2005 – Low Risk of Bias SYCAMORE 2017 – Low Risk of Bias ADJUVITE 2018 – Low Risk of Bias

Appendix 2: AMSTAR REVIEW

Renton *et al.* 2022[3] – Moderate Quality Review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	Yes
NRSI	
	Yes
	Yes
	Yes
	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	Yes
NRSI	
	Yes
	Yes
	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

Appendix 3: AGREE II ASSESSMENT SUMMARIES

AGREE II assessment scores																							
GKJR JIA TNF-i																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	5	2	2	5	1	2	5	4	2	6	3	3	5	3	5	5	6	3	4	1	2	3	3	80
Appraiser 2	7	6	6	3	1	5	6	5	5	6	7	7	6	1	5	7	7	1	1	1	1	5	5	104
Item Total	12	8	8	8	2	7	11	9	7	12	10	10	11	4	10	12	13	4	5	2	3	8	8	184
Domain Total	28			17			74								35			14				16		184
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	61%			31%			**60%**								81%			13%				50%		**49%**
Overall assessment:	Guidelines are not recommened for use in this context																							

AGREE II assessment scores																							
ACR Uveitis																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	6	7	7	7	7	5	6	7	6	5	6	2	7	7	7	6	6	1	3	7	7	136
Appraiser 2	7	7	7	7	7	7	7	7	7	7	7	6	7	4	7	7	7	4	5	1	1	4	6	136
Item Total	14	14	13	14	14	14	14	12	13	14	13	11	13	6	14	14	14	10	11	2	4	11	13	272
Domain Total	41			42			96								42			27				24		272
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	97%			100%			**83%**								100%			40%				83%		**84%**
Overall assessment:	Guidelines are recommened for use in this context																							

AGREE II assessment scores																							
SHARE 2018 JIA TNF-i																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	3	6	7	1	3	7	6	6	7	3	5	5	2	6	5	6	3	2	1	6	3	3	103
Appraiser 2	7	7	7	7	1	6	7	4	3	6	6	4	3	1	6	7	7	1	1	1	1	4	4	101
Item Total	14	10	13	14	2	9	14	10	9	13	9	9	8	3	12	12	13	4	3	2	7	7	7	204
Domain Total	37			25			75								37			16				14		204
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	86%			53%			**61%**								86%			17%				42%		**57%**
Overall assessment:	Guidelines are not recommened for use in this context																							

AGREE II assessment scores																							
PSO JIA TNF-i																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	3	4	6	1	5	7	2	1	7	1	3	2	2	6	6	7	4	4	1	2	1	1	82
Appraiser 2	7	6	6	4	2	7	7	6	4	7	6	5	1	1	6	7	5	1	4	1	1	1	1	96
Item Total	13	9	10	10	3	12	14	8	5	14	7	8	3	3	12	13	12	5	8	2	3	2	2	178
Domain Total	32			25			62								37			18				4		178
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	72%			53%			**48%**								86%			21%				0%		**47%**
Overall assessment:	Guidelines are not recommened for use in this context																							

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