

Biological Therapy in Noninfectious Pediatric Uveitis: A Systematic Review

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Purpose: Noninfectious pediatric uveitis is a potentially blinding disease often associated with systemic conditions. In cases of chronic anterior uveitis without adequate response to steroids and immunosuppressants, biological response modifiers would be viable therapeutic options. Still, evidence is lacking on the safety of the long-term use of these drugs in children. Therefore, this study aimed to evaluate the efficacy and safety of biological therapy to treat noninfectious pediatric uveitis.

Methods: A systematic review was performed to identify original studies involving biological therapy for children diagnosed with noninfectious uveitis. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification system.

Results: Nine studies involving 526 children were eligible. Adalimumab was superior to placebo in reducing inflammatory activity (risk ratio (RR) 3.21 [95% confidence interval (CI) 1.65–6.27]; $P = 0.0006$; $I^2 = 0\%$) and steroid use (RR 2.27 [95% CI 1.03–4.99]; $P = 0.04$; $I^2 = 0\%$, low-certainty evidence). There was no difference between adalimumab and placebo in the occurrence of systemic adverse events (RR 2.51 [95% CI 0.74–8.54]; $P = 0.14$; $I^2 = 48\%$) and local events (RR 1.15 [95% CI 0.46–2.88]; $P = 0.76$; $I^2 = 1\%$). There was no difference between adalimumab and infliximab in response to treatment (RR 1.18 [95% CI 0.69–2.03]; $P = 0.55$; $I^2 = 91\%$, very low-certainty evidence) and in the occurrence of adverse effects (RR 0.84 [95% CI 0.41–1.73]; $P = 0.64$; $I^2 = 18\%$, low-certainty evidence).

Conclusion: There is low to very-low evidence that biological therapy is effective and safe in managing noninfectious pediatric uveitis. Future large randomized trials may provide more substantial evidence to confirm these results.

Keywords: uveitis, children, biological therapy, systematic review

Introduction

Uveitis is an inflammatory disorder of the uveal tract that can result in vision loss and blindness.¹ It is rarer in children than in adults, accounting for 2–20% of all cases worldwide.² Pediatric uveitis is a topic of particular interest because of its diagnostic and therapeutic challenges.³ Children with uveitis are frequently asymptomatic; however, the ocular inflammatory activity is commonly anterior, bilateral, chronic, recurrent, and resistant to conventional treatment, increasing the risk of vision-threatening complications.^{3,4} Noninfectious cases account for 69–95% of total pediatric uveitis cases, with juvenile idiopathic arthritis being the most frequent etiology.^{5,6}

A step-wise treatment for pediatric noninfectious uveitis is essential to maintain inflammatory control and decrease the risk of the potential local and systemic side

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effects of drugs. A typical approach begins with topical and oral steroids, with the addition of other therapies, as needed.⁷

Systemic disease-modifying antirheumatic drug (DMARD) therapy is used early in cases of resistance to treatment or steroid dependence.^{3,4} The conventional DMARD of choice continues to be methotrexate (MTX).⁴ Biological therapies, such as adalimumab (TNF- α inhibitor) and other biologic DMARDs, have emerged as therapeutic alternatives but only as second options.^{4,7} Studies have reported the efficacy of biological therapy, especially anti-TNF- α agents, in chronic noninfectious uveitis.^{8–11} However, quality evidence on the safety of regular use of these drugs in children is lacking.^{9,10} Therefore, we performed an updated systematic review of the literature to assess the clinical efficacy of biological therapy in treating noninfectious pediatric uveitis.

Methods

This systematic review was developed according to the guidelines of the Cochrane Handbook for Systematic Intervention Reviews¹² and described according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.¹³

Eligibility Criteria

Randomized controlled trials (RCTs) and nonrandomized controlled studies (NRS) involving children under 18 years old with noninfectious uveitis, regardless of sex and type of associated systemic disease, were included. Interventions included any treatment regimen of biological therapy versus placebo, other drugs, or a combination of therapies. The primary outcome was the rate of satisfactory response to treatment, characterized by the reduction or resolution of ocular inflammatory activity in the anterior chamber and the occurrence of local and systemic adverse events. The secondary outcome included reduction in or interruption of the use of corticosteroids.

Data Source and Searches

Seven databases were searched in this review, including the Cochrane Central Register of Controlled Trials (CENTRAL; 1996 to March 2021), PubMed (1966 to March 2021), Web of Science (1900 to March 2021), EMBASE (1974 to March 2021), Latin American and Caribbean Literature in Health Sciences (LILACS; 1982 to March 2021), SCOPUS (2004 to March 2021), and

Clinical Trials (2008 to March 2021). Using the terms of the Medical Subject Headings (MeSH) and accessible terms related to “uveitis,” “tumor necrosis factor antagonist alpha,” and “child,” the search strategy was adapted and replicated for each database. There were no restrictions on language or publication year.

The proposed search strategy was as follows: [(uveitis or iritis or iridocyclitis or pars planitis or retinoblastoma or choroiditis or retinitis or Behcet or Vogt or Koyanagi or Harada or Fuchs or juvenile rheumatoid or juvenile idiopathic arthritis) and ((Tumor necrosis factor-alpha) or biologic therapy or biological therapies monoclonal antibodies or humanized monoclonal antibodies or Infliximab or Adalimumab or Etanercept or Certolizumab Pegol or Remicade or Humira or Enbrel or Golimumab or Simponi or Cimzia or (TNFR-Fc fusion protein)) and (child or children or pediatric or pediatrics or childhood) and (noninfectious)].

Study Selection and Data Extraction

Two authors independently screened the search results using research titles and, when available, abstracts. Then, according to pre-specified selection criteria, the full texts of the selected articles were retrieved and independently assessed for inclusion by two reviewers. Disagreement was resolved through consensus and consultation with a third author in case of any dissent.

The data from the included studies were independently extracted by two reviewers using a standard data extraction form with the following information: Study characteristics (design, methods of randomization), participants, interventions, and outcomes (types of outcome measures, adverse events).

Risk of Bias Assessment

The quality of RCTs was assessed using the “risk of bias” tool in Cochrane Collaboration,¹² which followed these criteria: Random sequence generation, allocation concealment, masking of participants and researchers, masking of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. For the analysis of NRS, the reviewers used another tool developed by Cochrane Collaboration,¹⁴ the “risk of bias in non-randomized studies of interventions” (ROBINS-I), which covers seven domains: Confusion, selection of participants, measurement of intervention, non-receipt of assigned intervention, losses, measurement of outcomes, and selective reporting of outcomes. When information

regarding the risk of bias or related to other aspects of the methodology was not available or clear, the reviewers tried to contact the authors of the studies to clarify doubts and obtain additional information. Two reviewers independently assessed the risk of bias in the included studies, and any disagreement was resolved through discussion or consensus involving all authors.

Certainty of Evidence

The GRADE methodology was adopted to determine the degree of certainty of evidence^{15,16} using five criteria: Global risk of bias, inaccuracy, inconsistency, indirect evidence, and publication bias. The degree of certainty for each result analyzed was classified as high, moderate, low, or very low. The results were summarized in an evidence profile. The reviewers lowered the degree of certainty of the evidence according to the influence of the assessment criteria.^{15,17}

Data Synthesis and Statistical Analysis

All outcomes were analyzed using dichotomous variables, combined Mantel–Haenszel RRs, and associated 95% confidence interval (CI) using random-effects models to data from three or more studies. The analyses were based on eligible patients who had reported outcomes in each study. Review Manager 5.3.5 (RevMan) software¹⁸ was used to perform all analyses. The variability of the results was estimated from the I^2 statistic and the p-value for the heterogeneity chi-square test. Heterogeneity was considered significant when $I^2 > 75\%$.¹²

Results

Study Selection

Figure 1 shows the process of identifying eligible studies. A total of 2384 citations were identified after removing duplicates. Through the screening based on titles and abstracts, 132 studies were found relevant to the subject. After full-text analysis, 34 were assessed for possible eligibility, of which 25 were excluded and 9 were included in the review consisting of 3 RCTs (Smith 2005, Quartier 2017 and Ramanan 2017)^{19–21} and 6 non-randomized studies (Tynjälä 2007, Simonini 2011, Zannin 2013, Gaidar 2014, Cecchin 2018, and Gunduz 2021),^{22–27} with a total of 526 participants included.

Study Characteristics

Table 1 describes the characteristics of the included studies, such as design, country, number of centers involved, length

of follow-up, number of participants, age, sex, intervention, and control. Three studies were conducted in Italy,^{23,24,26} one in France,²⁰ one in the United Kingdom,²¹ one in Finland,²² one in Russia,²⁵ one in Turkey,²⁷ and one in the USA.¹⁹ Three studies were conducted in a single center,^{19,25,27} and the other six studies were multicentric.^{20–24,26} The sample size of the included studies ranged from 12¹⁹ to 154²⁶ children. There was a predominance of females, and the average age ranged from 8.5²¹ to 15.2²⁷ years. The follow-up of the studies ranged from three²⁵ to fifty²⁷ months.

Regarding the type of intervention adopted, seven studies used adalimumab (Humira®, Abbott, Abbott Park, Green Oaks, IL, USA),^{20,21,23–27} and two studies used etanercept (Enbrel®, Pfizer, Pfizer Manufacturing Belgium NV, Puurs, ANR, Belgium).^{19,22} For the control group, six studies used infliximab (Remicade®, Janssen, Janssen Biotech, Titusville, NJ, USA),^{22–27} and three used placebo.^{19–21} In the studies involving a placebo group,^{19–21} for ethical reasons, all the children continued to receive pharmacological therapy, mainly methotrexate and corticosteroids. No child remained untreated.

Risk of Bias in the Included Studies

Figures 2 and 3 present the risk of bias in the studies included in the review. For RCTs, the main issues related to risk of bias were lack of information about the random sequence generation,¹⁹ allocation concealment,²⁰ masking of outcome assessment,¹⁹ and other biases (conflict of financial interest).²⁰ For NRS, the main issues related to risk of bias were confounding factors and the selection process of participants.^{22–27}

Intervention Effects

Anti-TNFα Agents versus Placebo

Three RCTs compared anti-TNFα agents versus placebo: Smith (2005) (etanercept), Quartier (2017) (adalimumab), and Ramanan (2017) (adalimumab).^{19–21} For the primary outcomes, anti-TNFα agents improved the chances of a satisfactory response to treatment compared to placebo ((RR 2.57 [95% CI 1.39–4.74]; $P = 0.003$; three studies; two drugs, $I^2 = 4\%$) (Figure 4) and (RR 3.21 [95% CI 1.65–6.27]; $P = 0.0006$; two studies; one drug; $I^2 = 0\%$) (Figure 5)).

Two RCTs^{20,21} reported systemic severe adverse events with adalimumab; however, there was no difference compared to placebo (RR 2.51 [95% CI 0.74–8.54]; $P = 0.14$; $I^2 = 48\%$). Regarding local adverse effects, there was also no difference between adalimumab and placebo (RR 1.15 [95% CI 0.46–2.88]; $P = 0.76$; $I^2 = 1\%$).

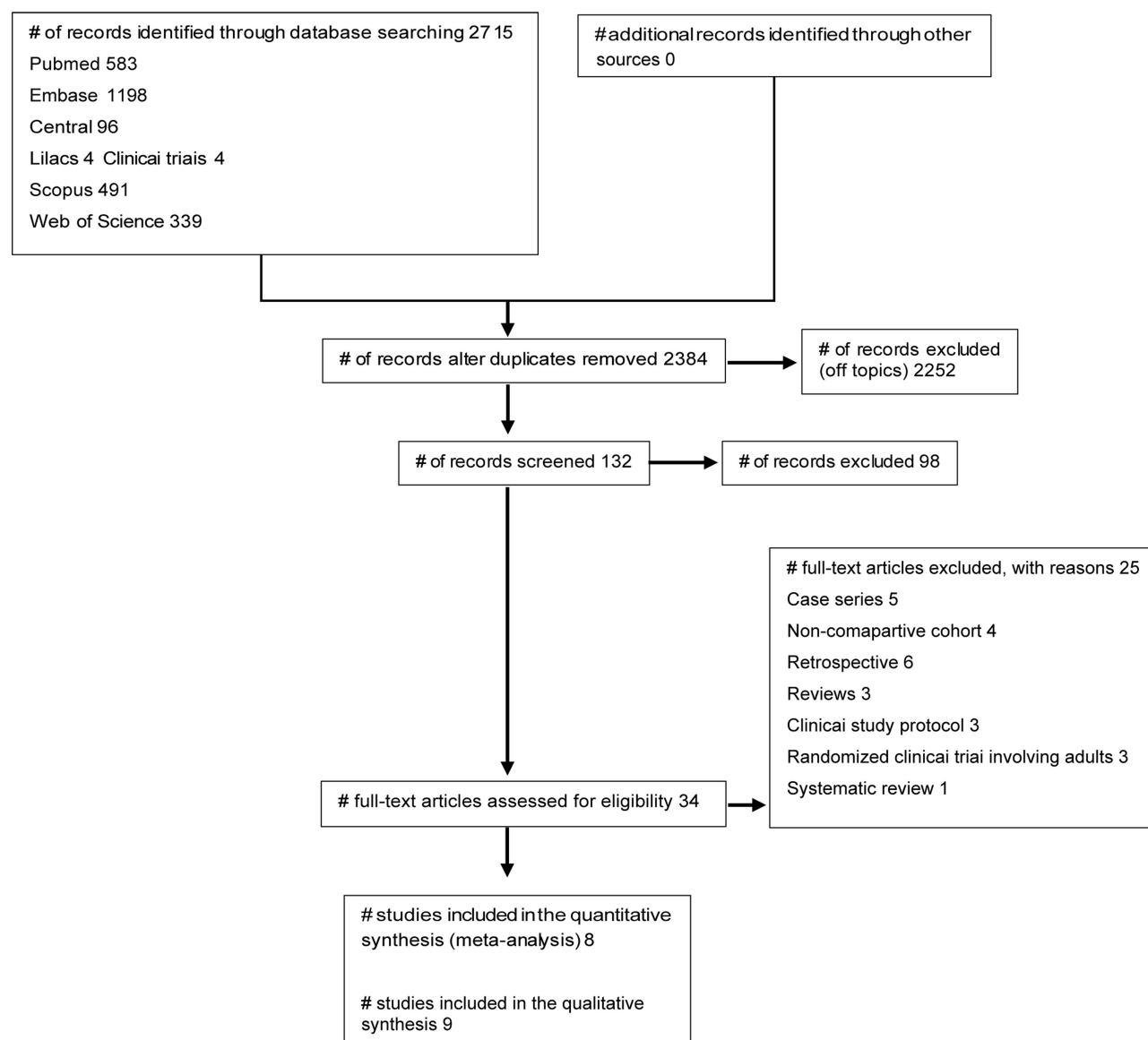


Figure 1 Review flowchart.

For the secondary outcome, adalimumab increased the chance of reducing or interrupting corticosteroid use compared to placebo (RR 2.27 [95% CI 1.03–4.99]; $P = 0.04$; $I^2 = 0$) (Figure 6).

Adalimumab versus Infliximab

Five NRS compared adalimumab and infliximab (Simonini 2011,²³ Zannin 2012,²⁴ Gaidar 2014,²⁵ Cecchin 2018,²⁶ and Gunduz 2021²⁷). Regarding primary outcomes, the analysis evidenced no difference between the two anti-TNF- α agents concerning a satisfactory response to treatment (RR 1.18 [95% CI 0.69–2.03]; $P = 0.55$, five studies; $I^2 = 91\%$) (Figure 7) and the occurrence of local and systemic adverse events

(RR 0.84 [95% CI 0.41–1.73]; $P = 0.64$, four studies; $I^2 = 18\%$) (Figure 8).

No study reported a reduction in or interruption of corticosteroid use in this comparison.

Figures 9–Figure 13 summarize findings for the main comparisons according to the GRADE classification. The certainty of the evidence of the outcomes varied from very low to low quality.

Discussion

Main Findings

This review sought to address the uncertainties regarding biological therapy in children with noninfectious uveitis.

Table 1 Characteristics of the Included Studies

Study	Type	Center	Local	Follow-Up (Months)	Age (Average or Age Group)	Sex (F/M)	Intervention	N	Dose	Control	N	Dose
Quartier 2017 ²⁰	RCT	9	France	12	10.8 ADA 9.2 PL	28/3	ADA	16	40mg/m ² > 13y 24 mg/m ² < 13y	Placebo	15	NR ^b + MTX (0.3–0.6 mg/Kg without exceeding 25mg/w)
Ramanan 2017 ²¹	RCT	14	United Kingdom	24	9.07 ADA 8.56 PL	70/20	ADA	60	40 mg/m ² >30Kg 20 mg/m ² <30Kg	Placebo	30	0.8mL + MTX (10–20 mg/m ² without exceeding 25mg/w)
Smith 2005 ¹⁹	RCT	1	USA	12	11	9/3	ETA	7	0.4 mg/Kg	Placebo	5	NR ^b + MTX (≤ 1 mg/Kg/w without exceeding 25mg/w) or PD (≤ 1 mg/Kg/d)
Cecchin 2018 ²⁶	NRS P	24	Italy	24	9.5	1/4,3	ADA	95	1 mg/kg	IFX	59	5 mg/Kg
Simonini 2011 ²³	NRS P	3	Italy	12–40	9.2	22/11	ADA	16	24 mg/m ²	IFX	17	5 mg/Kg
Zannin 2013 ²⁴	NRS P	NR ^a	Italy	12	9.7	71/20	ADA	43	1 mg/Kg (máx 40mg)	IFX	48	5 mg/Kg
Tynjälä 2007 ²²	NRS R	3	Finland	24	9.8	39/8	ETA	24	0.4 mg/Kg	IFX	21	3–6 mg/Kg
Gaidar 2014 ²⁵	NRS R	1	Russia	3–48	5–17	27/10	ADA	28	40 mg/m ²	IFX	9	5–6 mg/Kg
Gunduz 2021 ²⁷	NRS R	1	Turkey	12–50	12.5 ADA 15.2 IFX	19/14	ADA	17	40 mg ≥ 30 Kg 20 mg < 30 Kg	IFX	16	5 mg/Kg

Notes: ^aMulti-center (number not reported). ^b(placebo dose not reported).

Abbreviations: RCT, randomized clinical trial; P, prospective; R, retrospective; PL, placebo; ADA, adalimumab; IFX, infliximab; ETA, etanercept; NR, not reported; NRS, non-randomized study; PD, prednisone; MTX, methotrexate.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Quartier 2017 ²⁰	+	?	+	+	+	+	-
Ramanan 2017 ²¹	+	+	+	+	+	+	+
Smith 2005 ¹⁹	?	+	+	?	+	+	+

Figure 2 Summary of risk of bias from randomized clinical trials. Review the authors' judgments about each item of risk of bias for each study included in the meta-analysis.

Despite their high cost, these drugs, especially infliximab and adalimumab, represent a new strategy in the long-term control of the visual outcomes and ocular complications in refractory uveitis.

The meta-analysis demonstrated that anti-TNF α agents are more effective than placebo and maintained the corticosteroids or traditional DMARDs already used by children in reducing ocular inflammatory activity. Adalimumab in monotherapy improved the chances of a satisfactory response to treatment; however, it had similar effectiveness to infliximab. However, the benefits of etanercept cannot be evaluated because of methodological differences between the two included RCTs that used the drug.^{19,22}

Regarding adverse events, the results suggested that adalimumab has a good long-term safety profile and can effectively reduce or interrupt corticosteroid therapy.

These results can help choose the best treatment logistics, improving clinical care for children with chronic and refractory noninfectious uveitis.

Applicability and Quality of Evidence

Regarding the applicability of evidence, the use of anti-TNF- α in clinical practice is still limited by high costs and restricted access. In the developing world, more affordable

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Tynjälä 2007 ²²	⊖	⊖	⊕	⊕	⊖	⊕	⊕	⊖
	Simonini 2011 ²³	⊖	⊖	⊕	⊖	⊕	⊕	⊕	⊖
	Zannin 2013 ²⁴	⊖	⊖	⊕	⊖	⊕	⊕	⊕	⊖
	Gaidar 2014 ²⁵	⊖	⊖	⊖	⊖	⊕	⊖	⊕	⊖
	Cecchin 2018 ²⁶	⊖	⊖	⊕	⊕	⊖	⊕	⊕	⊖
	Gunduz 2021 ²⁷	⊖	⊖	⊕	⊖	⊕	⊕	⊕	⊖
Domains:		Judgement							
D1: Bias due to confounding.		⊖ Moderate							
D2: Bias due to selection of participants.		⊕ Low							
D3: Bias in classification of interventions.									
D4: Bias due to deviations from intended interventions.									
D5: Bias due to missing data.									
D6: Bias in measurement of outcomes.									
D7: Bias in selection of the reported result.									

Figure 3 Summary of risk of bias from non-randomized controlled trials.

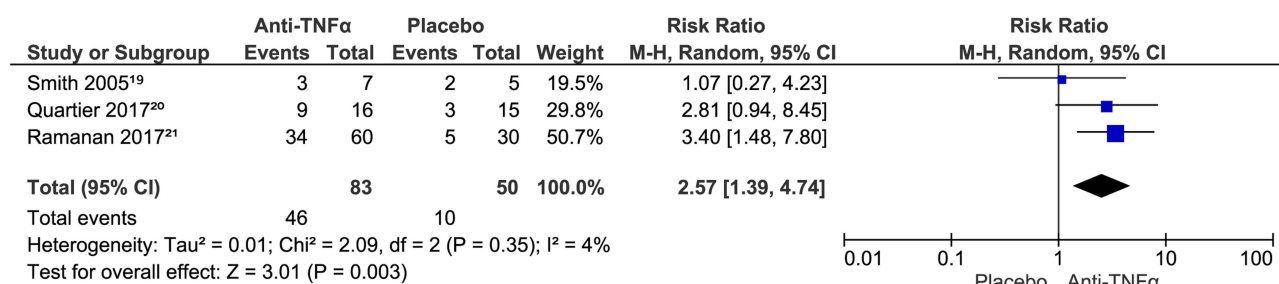


Figure 4 Comparison: Anti-TNF- α versus placebo. Outcome: Satisfactory response rate to treatment.

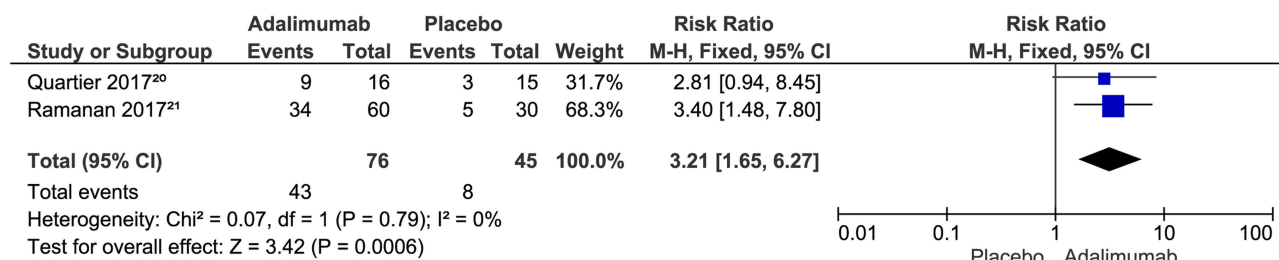


Figure 5 Comparison: Adalimumab versus placebo. Outcome: Satisfactory response rate to treatment.

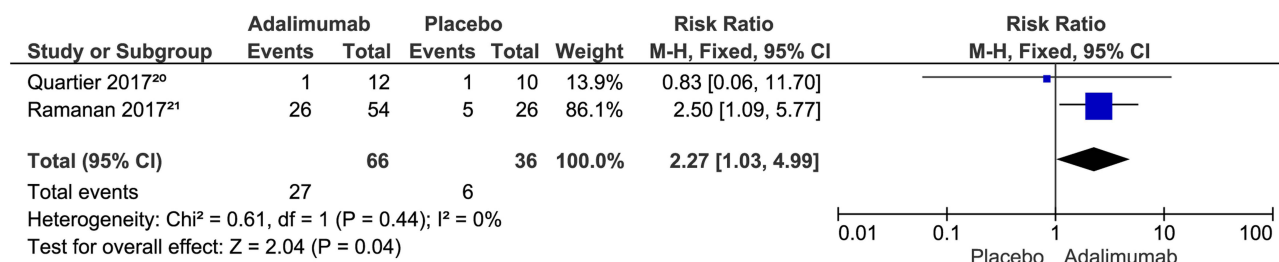


Figure 6 Comparison: Adalimumab versus placebo. Outcome: Reduction or interruption of the use of corticosteroids.

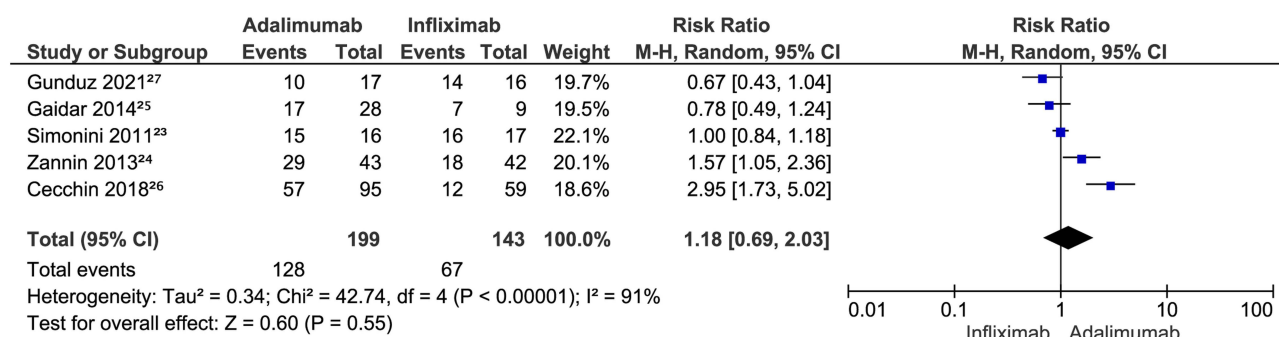


Figure 7 Comparison: Adalimumab versus infliximab. Outcome: Satisfactory response rate to treatment.

drugs such as corticosteroids^{28,29} and immunosuppressants³⁰ are the most viable therapeutic options. In these countries, however, the cost-benefit discussion on adalimumab has divided opinions. Hughes et al reported that in the United Kingdom, adalimumab does not currently represent a cost-

effective treatment option for the public health system.³¹ Other authors, however, opposed the conclusions of the study, contesting the methodology used and emphasizing the lack of therapeutic options in cases of resistance to methotrexate, with the same clinical efficacy as

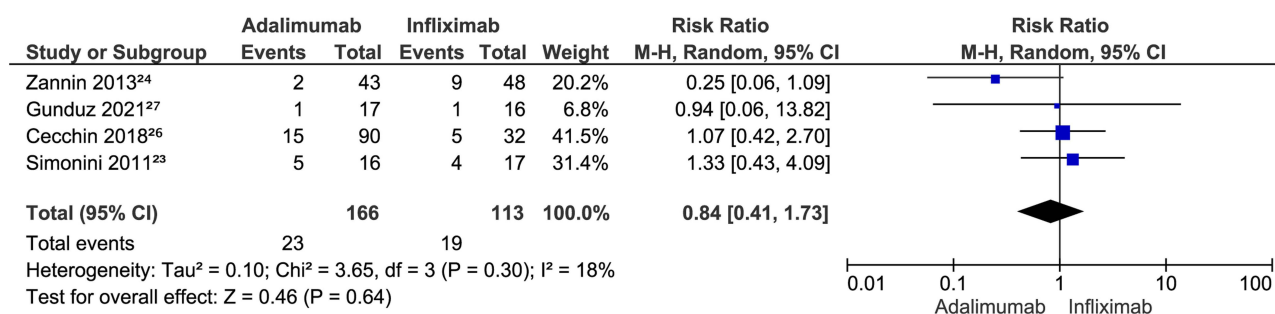


Figure 8 Comparison: Adalimumab versus infliximab. Outcome: occurrence of local and systemic adverse events.

Summary of findings:

Anti-TNF α compared to Placebo in Children with non-infectious uveitis

Patient or population: Children with non-infectious uveitis

Setting: Population based in communities in France, UK and USA

Intervention: Anti-TNF α

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Anti- TNF α				
Satisfactory Response to Treatment	200 per 1,000	514 per 1,000 (278 to 948)	RR 2.57 (1.39 to 4.74)	133 (3 RCTs)	$\oplus\oplus\circ\circ$ LOW ^{a,b}	

*The risk in the intervention group (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).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgrade to imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

b. Downgrade to publication bias due to external financial benefit and relatively short follow-up period.

Figure 9 Summary of findings for the comparison of anti-TNF- α versus placebo. Outcome: Satisfactory response to treatment.

adalimumab.^{32,33} In the present review, only one study (Ramanan 2017²¹) reported data on quality of life and the cost-effectiveness of treatment.

The evidence on the action of anti-TNF- α agents will be reinforced soon with the results of clinical trials in progress. We highlight the RCT (NCT03828019) in the recruitment stage, which aims to compare the clinical efficacy of adalimumab with that of conventional immunosuppressive therapy, which is expected to end in 2023.

The methodological quality of the included RCTs was, in general, classified as having a low risk of bias while that of NRS as having moderate risk. Quality of evidence, meanwhile, varied from very low to low; that is, confidence in the estimated effect is limited, and the actual

effect may be substantially different from the estimated effect.

Relation to Prior Work

A systematic review that is relevant to our objectives was published in 2014. Simonini et al³⁴ included 22 retrospective studies, and only one RCT was excluded in the analysis. Furthermore, the authors did not use the GRADE classification to assess the certainty of the evidence. The authors concluded that the results based on retrospective studies did not have the strength yet to change the level of recommendation of anti-TNF α agents for noninfectious uveitis in children. Therefore, with the results of this review, there is already evidence that supports the use of

Summary of findings:

Adalimumab compared to Placebo for Children with non-infectious uveitis

Patient or population: Children with non-infectious uveitis**Setting:** Population based in communities in France and UK**Intervention:** Adalimumab**Comparison:** Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Adalimumab				
Satisfactory Response to Treatment	178 per 1.000	571 per 1.000 (293 to 1.000)	RR 3.21 (1.65 to 6.27)	121 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	

*The risk in the intervention group (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).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgrade to imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

b. Downgrade to publication bias due to external financial benefit and relatively short follow-up period.

Figure 10 Summary of findings for the comparison of adalimumab versus placebo. Outcome: Satisfactory response to treatment.

Summary of findings:

Adalimumab compared to Placebo for Children with non-infectious uveitis

Patient or population: Children with non-infectious uveitis**Setting:** Population based in communities in France and UK**Intervention:** Adalimumab**Comparison:** Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Adalimumab				
Reduction or Discontinuation of the Use of Systemic or Topical Corticosteroids	167 per 1.000	378 per 1.000 (172 to 832)	RR 2.27 (1.03 to 4.99)	102 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	

*The risk in the intervention group (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).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgrade to imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

b. Downgrade to publication bias due to external financial benefit and relatively short follow-up period.

Figure 11 Summary of findings for the comparison of adalimumab versus placebo. Outcome: Reduction or discontinuation of corticosteroids use.

Summary of findings:

Adalimumab compared to Infliximab in Children with non-infectious uveitis**Patient or population:** Children with non-infectious uveitis**Setting:** Population based in communities in Italy, Russia and Turkey**Intervention:** Adalimumab**Comparison:** Infliximab

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Infliximab	Risk with Adalimumab				
Satisfactory Response to Treatment	469 per 1.000	553 per 1.000 (323 to 951)	RR 1.18 (0.69 to 2.03)	342 (5 observational studies)	⊕○○○ VERY LOW a,b,c	

*The risk in the intervention group (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).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgrade to global risk of bias because there was no randomization, allocation strategy, concealment of allocation and masking of participants, researchers and outcome evaluators.

b. Downgrade to inconsistency because $I^2 = 91\%$.

c. Downgrade to imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

Figure 12 Summary of findings for the comparison of adalimumab versus infliximab. Outcome: Satisfactory response to treatment.

Summary of findings:

Adalimumab compared to Infliximab for Children with non-infectious uveitis**Patient or population:** Children with non-infectious uveitis**Setting:** Population based in communities in Italy and Turkey**Intervention:** Adalimumab**Comparison:** Infliximab

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Infliximab	Risk with Adalimumab				
Adverse Event Rate	168 per 1.000	141 per 1.000 (69 to 291)	RR 0.84 (0.41 to 1.73)	279 (4 observational studies)	⊕⊕○○ LOW ^{a,b}	

*The risk in the intervention group (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).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgrade to global risk of bias because there was no randomization, allocation strategy, concealment of allocation and masking of participants, researchers and outcome evaluators.

b. Downgrade to imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

Figure 13 Summary of findings for the comparison of adalimumab versus infliximab. Outcome: Local and systemic adverse events.

these agents in pediatric uveitis. Although equality of evidence still indicates the need for more randomized studies to increase the strength of the recommendation, biological therapy is consolidating itself as a viable option in the treatment of noninfectious pediatric uveitis.

Strengths and Limitations

The review has several strengths, including extensive, sensitive, and critical literature research, with no language restrictions or publication status. The analysis of the strength of the evidence through the GRADE system^{15,16} and risk of bias of NRS through the ROBINS-I tool¹⁴ were also differential.

The main limitations were the reduced number of included studies, the moderate risk of bias of NRS, and the high heterogeneity observed in a meta-analysis with NRS (91%).

The certainty of evidence of the outcomes ranged from very low to low. Classification downgrading occurred mainly because of methodological flaws in NRS, imprecision, heterogeneity, and publication bias.

Conclusion

In conclusion, there is evidence that anti-TNF α drugs are viable therapeutic options in clinical practice and are effective in controlling inflammation and reducing corticosteroid therapy in noninfectious refractory pediatric uveitis to standard treatment. The evidence for the similar efficacy of adalimumab and infliximab lacks solid evidence since the existing ones were generated from NRS. More RCTs are still needed, comparing the various anti-TNF α drugs available, with methodological quality, standardized outcomes, and adequate sample size to confirm and increase the certainty of evidence found in this review.

Disclosure

None of the authors has any potential conflict of interest to disclose.

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