Efficacy and Safety of Anti-TNFα Therapy for Uveitis Associated with Juvenile Idiopathic Arthritis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: To investigate the efficacy and safety of anti-TNFα therapy in patients with juvenile idiopathic arthritis associated uveitis (JIA-U).

Methods: Embase, PubMed, Cochrane Library, and Web of Science were systematically searched for studies reporting anti-TNFα treatment in patients with JIA-U. The primary outcome was the control of intraocular inflammation (CII). The pooled proportion of CII was assessed by the random-effects method when $I^2 > 50\%$, otherwise, by the fixed-effect method. This study was registered with PROSPERO (CRD42020161749).

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Results: Three randomized clinical trials (RCTs), twelve case series, three retrospective cohort studies, and three case reports were identified. A total of 399 patients were receiving anti-TNFα therapy, of which 201 patients were treated with adalimumab (ADA), 139 with infliximab (IFX), 36 with etanercept (ETA), 20 with golimumab (GLM), and 3 with certolizumab pegol (CZP). The pooled proportions of CII on observational studies were 82% (95% CI 63–96%) in patients receiving ADA, 56% (95% CI 30–80%) in IFX, 38% (95% CI 8–73%) in ETA and 65% (95% CI 42–86%) in GLM, respectively. All three patients treated with CZP reached improved activity. ADA therapy led to a significantly higher proportion of CII compared to IFX therapy ($\chi^2 = 26.24$, $P < 0.001$), or to ETA therapy ($\chi^2 = 13.43$, $P < 0.001$); but no statistical difference was observed between IFX and ETA ($\chi^2 = 0.13$, $P = 0.71$). As to safety, most reported adverse events were tolerable and two cohort studies consistently showed that ADA was safer than IFX.

Conclusions: The existing evidence suggests that ADA is better than IFX regarding efficacy and safety. The effectiveness of IFX is higher than ETA with no statistical difference. GLM and CZP may be proxies for ADA but the evidence is limited.

Key Summary Points

Why carry out this study?

Juvenile idiopathic arthritis(JIA) is the commonest rheumatic disease in children and uveitis is the commonest extra-articular manifestation of it. JIA associated uveitis(JIA-U) is still a big challenge for pediatric rheumatologists and ophthalmologists due to its insidious onset, sight-threatening complications and high refractory risk. In those who are refractory to topical glucocorticoids and methotrexate, anti-tumor necrosis factor α (anti-TNFα) therapy is recommended by guidelines nowadays. However, high quality evidence of which anti-TNFα drug to choose and whether the choice is safe is still lacking.

Thus, a systematic review and meta-analysis was conducted to evaluate the efficacy and safety of anti-TNFα therapy in the treatment of JIA-U.

What was learned from the study?

The existing evidence suggests that adalimumab is the best anti-TNFα therapy for JIA-U treatment. Adalimumab is significantly better than infliximab and etanercept in the control of intraocular inflammation. Adalimumab is also better than infliximab in improving visual acuity and remaining in remission.

The efficacy of infliximab is higher than etanercept but with no statistical difference. Golimumab and certolizumab pegol may be proxies for adalimumab, but further evidence is needed.

Most reported adverse events of anti-TNFα therapy were tolerable. Some severe adverse events were reported but malignancy wasn't seen during the JIA-U treatment.

DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13953848.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the commonest rheumatic diseases in children. Uveitis is the commonest extra-articular manifestation of JIA and can develop even before the onset of arthritis [1]. Among all etiologies of uveitis in children, JIA accounts for a proportion ranging from 15 to 67% in Europe, North America, and Israel [2]. Uveitis can occur in different subtypes of JIA. Female gender, younger age of disease onset, oligoarthritis and antinuclear antibody (ANA) positivity are the main risk factors for the development of uveitis [1, 3, 4]. Anterior uveitis is the commonest (83%) anatomical type associated with JIA, which includes acute anterior uveitis (AAU) and chronic anterior uveitis (CAU). AAU is typically associated with HLA–B27 and occurs in children with enthesitis-related or psoriatic arthritis. It often presents with overt symptoms, while generally doesn't need systemic treatment [5]. CAU is the commonest type of JIA-U and frequently associated with oligoarticular and rheumatoid factor negative polyarticular subtypes of JIA. The onset of CAU is usually insidious and mostly asymptomatic. Uncontrolled CAU can result in sight-threatening complications such as cataracts, glaucoma and even vision loss. In light of this, screening JIA patients regularly for uveitis is currently emphasized [6–8].

At present, a stepwise therapy strategy is adopted for children with JIA associated CAU. The initial treatment is topical glucocorticoids. In those who are refractory to or dependent on topical glucocorticoids, methotrexate is always used, followed by anti-tumor necrosis factor α (anti-TNFα) biologic therapy [9, 10]. For severe active CAU and sight-threatening complications, the combination of methotrexate and

anti-TNFα is conditionally recommended over methotrexate monotherapy by the American College of Rheumatology/Arthritis Foundation [7]. ETA is the first approved anti-TNFα biologic by the U.S. Food and Drug Administration for the treatment of JIA. As a greater incidence of new-onset uveitis is associated with ETA treatment than is seen with either ADA or IFX therapy [11], ETA is now generally not recommended for the treatment of pediatric uveitis. Instead, either ADA or IFX is recommended as the preferred agent, but evidence is not conclusive [7, 10, 12–14]. And it's still unclear which drug is the best and whether the choice is safety.

Thus, we herein performed a systematic review and meta-analysis to evaluate the efficacy and safety of anti-TNFα therapy in the treatment of JIA-U.

METHODS

Information Sources and Search Strategy

This study was performed following a predefined protocol registered with PROSPERO (CRD42020161749) and fully complied with PRISMA guidelines [15]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. A systematic search of Embase, PubMed, the Cochrane Library, and Web of Science was performed for relevant articles published from the commencement to 1 November 2019. The keywords comprised "JIA" or "JRA" or "juvenile rheumatoid arthritis" or "arthritis and (child* or kid)" crossed with "uveitis" or "JIAU" or "juvenile idiopathic arthritis associated uveitis", which were then crossed with "anti-tumor necrosis factor-alpha" or "anti-TNFα" or "etanercept" or "Enbrel" or "adalimumab" or "Humira" or "infliximab" or "Remicade" or "golimumab" or "Symponi" or "certolizumab pegol" or "Cimzia". The search strategies are shown in Supplementary Data S1.

Eligibility Criteria

To be eligible, studies were required: (1) to be focused on JIA-U; (2) to report data on patients with JIA onset at or before age 16; (3) to be starting one of the available anti-TNFα treatments for JIA-U with an inadequate response to topical steroids and DMARDs; (4) to include outcome measures assessing the efficacy or safety of anti-TNFα treatment; (5) to have at least a three-month follow-up; (6) to be published in English.

Outcome Measures

The primary outcome measure was the CII which mainly includes "improved activity" and "remission" according to Standardization of Uveitis Nomenclature (SUN) Working Group criteria [16]. Improved activity is a two-step decrease in the level of inflammation or decreases to grade 0. Remission means inactive disease for 3 months after discontinuing all treatments for eye disease. Besides, some studies adopted other definitions, such as a 30% reduction of inflammation on laser flare photometry, no relapse, etc. For a comprehensive analysis, we included all of these studies. As for secondary outcome measures, we considered the control of visual acuity (VA), and corticosteroid-sparing. Improved visual acuity was defined as a doubling of the visual angle in at least 1 eye which equals three lines on a decimal scale [17]. As for the definition of corticosteroid-sparing, it was defined as a decrease by more than 50%, or reductions to below ≤ 0.1 mg/kg, or cessation of daily corticosteroid use [18]. Safety was assessed by the occurrence of adverse effects (AEs) and serious adverse effects (SAEs).

Study Selection and Data Collection

Firstly, two reviewers independently eliminated duplicates and irrelevant studies by reading the titles and abstracts. When abstract information was not enough to make a decision, we retrieved the full text further. For a comprehensive analysis, we not only included RCTs, cohort studies but also included qualified case

series and case reports. Review papers, meta-analysis, editorial letters, and expert opinions were excluded to avoid duplication. Discrepancies in the process of study screening were resolved by discussion or consulting a third person. Data were extracted by one reviewer according to a standard form, and checked by a second reviewer.

Risk of Bias in Individual Studies

The Cochrane Collaboration risk of bias tool [19] was used to evaluate RCT from seven aspects: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome; incomplete outcome data; selective reporting and other unclear bias. The Revman software (Version 5.3) was used to visualize the results. The Newcastle–Ottawa Scale was applied to assess the risk of bias in cohort studies [20, 21]. Studies scoring ≥ 5 and ≤ 8 were designated as low risk of bias, ≥ 3 and ≤ 4 as moderate and ≤ 2 as high. JBI critical appraisal checklists were used to assess the quality of case reports and case series [22].

Statistical Analysis

For the first outcome measure, we calculated the pooled proportions and 95% confidence intervals (CIs). Heterogeneity across studies was measured by Cochrane's χ^2 test and I^2 statistics [23]. $I^2 > 50\%$, $p < 0.1$ was regarded as statistically significant, then the random-effects model was used to present the pooled results, otherwise, a fixed-effect model (Mantel–Haenszel method) was used [19]. The pooled results were visualized with forest plots. The funnel plots were used to detect publication bias and heterogeneity. A Chi-square test was performed to determine whether there are statistical differences between the efficacy of ADA, IFX, and ETA. All the statistical analyses were conducted by R software (version 4.0.2).

RESULTS

Study Selection and Characteristics

A total of 1175 articles were retrieved by a computerized search. After 289 duplicates were automatically identified by Endnote, we excluded a further 813 studies by screening titles and abstracts. After assessing the full text of the remained 73 studies, we excluded another 52 studies. Overall, 21 articles were eligible: 10 on ADA, 7 on IFX, 3 on ETA, 2 on GLM, and 1 on CZP therapy. The reasons why other articles were excluded were shown in Fig. 1.

The majority of the included studies were retrospective case series with 12 articles. The rests were 3 RCTs, 3 retrospective cohort studies and 3 case reports. Table 1 showed the main characteristics of the 21 eligible articles. A total of 531 patients were included and 399 patients received anti-TNFα therapy. Of them, 201 received ADA, 139 received IFX, 36 received ETA, 20 received GLM, and 3 received CZP. Two articles did not reveal the patient gender [24, 25], and there were 293 (61.6%) females in the remaining studies. Most studies included more women than men, except for one article[26]. The patients were followed up from 6 to 42.4 months with an average length of follow-up being 20.1 months.

Risk of Bias within Studies

Regarding three RCTs, a study conducted by Ramanan et al. [27] had a low risk of bias in all items. The other two studies [28, 29] had an unclear risk of bias in allocation concealment and blinding of outcome assessment. The study conducted by Janine A. Smith et al. [29] had another unclear risk of bias in randomization. All the three cohort studies were regarded as low risk of bias, of which two had a score of 8 out of 9 and the other one had a score of 7. As for case reports and case series, all the studies were considered qualified assessed by JBI critical appraisal. A summary of the quality assessments was presented in the Supplementary Table S1.
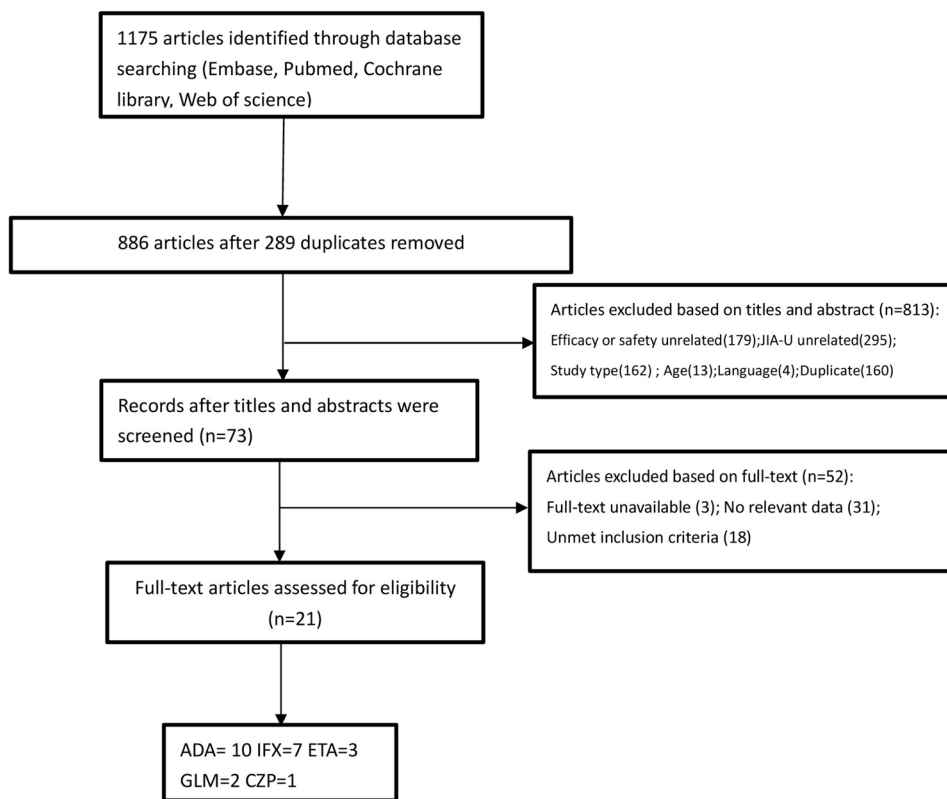
Fig. 1 The flow diagram of literature identification. *ADA* adalimumab, *IFX* infliximab, *ETA* etanercept, *GLM* golimumab, *CZP* certolizumab pegol

Control of Intraocular Inflammation

After the analysis, the pooled proportion of CII was 82% (95% CI 63–96%), 56% (95% CI 30–80%) and 38% (95% CI 8–73%) for the treatment of ADA, IFX and ETA, respectively. The results were shown by forest plots in Fig. 2. Because of the obvious heterogeneity, we chose the random-effects model to present the pooled results. The funnel plots showed the possible publication bias and heterogeneity in ADA, IFX and ETA (Fig. 3). We performed the Chi-square test to investigate the differences between ADA, IFX, and ETA. As demonstrated in Table 2, the CII proportion of ADA was much higher than that of IFX ($\chi^2 = 26.24$, $P < 0.001$) and ETA ($\chi^2 = 13.43$, $P < 0.001$), whereas no significant difference was indicated between IFX and ETA ($\chi^2 = 0.13$, $P = 0.71$). For GLM, the pooled proportion was 65% (95% CI 42–86%). Only one qualified article containing three patients was

retrieved for CZP treatment, and all three patients reached the criteria of SUN improved activity.

As for visual acuity, seven articles [30–36] were available for the analysis. Improved or stable VA was reported in 12 (92.3%) out of 13 patients with ADA treatment, 9 (90.0%) of 10 with IFX, 9 of 12 (75.0%) with ETA, 13 (100.0%) of 13 with GLM. In addition, two studies [29, 32] provided information regarding logMAR (logarithm of the minimum angle of resolution) and BCVA (best-corrected visual acuity). Quartier et al. [29] reported that the logMAR changed from 0.1 to 0.15 after ADA therapy. Palmou-Fontana et al. [32] reported that the BACV changed from 0.5 to 0.62 after IFX treatment.

Information on corticosteroid-sparing was extractable in nine of the eligible articles. The steroid-sparing, even discontinuation, was achieved in 26 (72.2%) of 36 patients with ADA treatment, in 10 (100%) of 10 patients with IFX

Table 1 Basic characteristics of the studies included

Source	Study type	Patients	Treatment group (no. of participants, F/M)	Control group (no. of participants, F/M)	Age, years	Length of follow-up (months)	Control of intraocular inflammation (TG vs CG)	Visual acuity	Corticosteroid sparing (TG vs CG)	AEs and SAEs (TG vs CG)
Ramanan, et al. [27] (EudraCT number, 2010–021,141-41)	RCT, DB	90	ADA (60, 47/13) 20 mg/0.8 ml for participants weighing < 30 kg or 40 mg/0.8 ml for participants weighing ≥ 30 kg	Placebo (30, 23/7)	8.9	18	Number of participants failing treatment (14/60 vs 17/30) (RR 0.40, 95% CI 0.23–0.72; $P = 0.002$)	NA	4/7vs2/2	AEs 59 vs 26 The rate of AEs (10.60 per PY, 95% CI 9.77–11.44 per PY)vs (7.12 per PY, 95% CI 5.89–8.53 per PY) SAEs 13 vs 2 The rate of SAEs (0.29 per PY vs 0.19 per PY)
Quartier et al. [28] (Trial registration number: NCT01385826)	RCT, DB	31	ADA (16, 15/1) 24 mg/m^2 in patients aged < 13 years, 40 mg in the others, every other week	Placebo (15, 13/2)	9.5 (4.9–29.1)	12	30% reduction of Inflammation on LFP: 9/16 vs 3/15 ($P = 0.038$, χ^2 test; RR = 2.81, 95% CI 0.94–8.45; RD = 36.3%, 95% CI 2.1–60.6);	logMAR: 0.1 (− 0.2 to 1.3) to 0.15 (− 0.10 to 1.10)	NA	NA
Janine A. Smith et al. [29] (Trial registration number: NCT00012506)	RCT, DB	12	ETA (7, 4/3) 0.4 mg/kg to a maximum of 25 mg subcutaneously twice weekly for 6 months	Placebo (5, 5/0)	11 (6–15)	6	AC cells to 0 or topical corticosteroid < 3 times/day or 50% reduction in number or dose of other anti-inflammatory medications: 3 (95% CI 0.10–0.82) vs 2 (95% CI 0.05–0.85) ($P = 1.0$)	NA	0/2vs0/2	AEs: 5 vs 3 $P > 0.5$ minor infections 71% vs 60% ($P = 0.58$) No SAEs
Eachempati, et al. [50]	Retrospective case report	1	IFX (1, 1/0) four-weekly infliximab infusions at a dose of 6 mg/Kg	NA	15	NA	NA	NA	NA	SAE:1 transient acute coronary syndrome and arrhythmias

Table 1 continued

Source	Study type	Patients	Treatment group (no. of participants, F/M)	Control group (no. of participants, F/M)	Age, years	Length of follow-up (months)	Control of intraocular inflammation (TG vs CG)	Visual acuity	Corticosteroid sparing (TG vs CG)	AEs and SAEs (TG vs CG)
Clement et al. [33]	Retrospective case series (conference abstract)	8	ADA (8, 5/3) 40 mg/m² every 2 weeks	NA	10	17.4	NA	Stable 7, improved 1	NA	No AEs and SAEs
Cecchin et al. [26]	Retrospective cohort study	154	ADA (95, 16/79) subcutaneously every 2 weeks at a dosage of 1 mg/kg (max 40 mg)	IFX (59, 15/44) 5 mg/kg, 0, 2, 6, and 12 weeks, and then every 6–8 weeks	9.5 (5.2 uveitis onset)	24	Clinical remission: the absence of flares for > 6 months on systemic treatment, with or without minimal topical treatment:57vs12	NA	NA	AEs:15 vs 5 (10.6/100 PY vs 25.0/100 PY) ADA: 7 infections; 1 infusion reactions; 11 systemic symptoms IFX: 8 infections; 1 infusion reactions; 7 systemic symptoms No SAEs
Lazarević et al. [46]	Retrospective case series	11 Two subtypes: oligoarticular or enthesitis-related JIA 3vs8	ADA (11, 8/3) 24 mg/m² in two weeks intervals	NA	14.5 (9–18)	24	No relapse:11	NA	NA	No AEs and SAEs
Alicia et al. [30]	Retrospective case series	5	ADA (5, 4/1) 24 mg/m² every 2 weeks subcutaneously, (maximum dose 40 mg)	NA	11.8	40.6	SUN improved activity: 5	Improved 1 Stable 3 Worse 1	NA	AEs:2 Appendicitis Varicella No SAEs

Table 1 continued

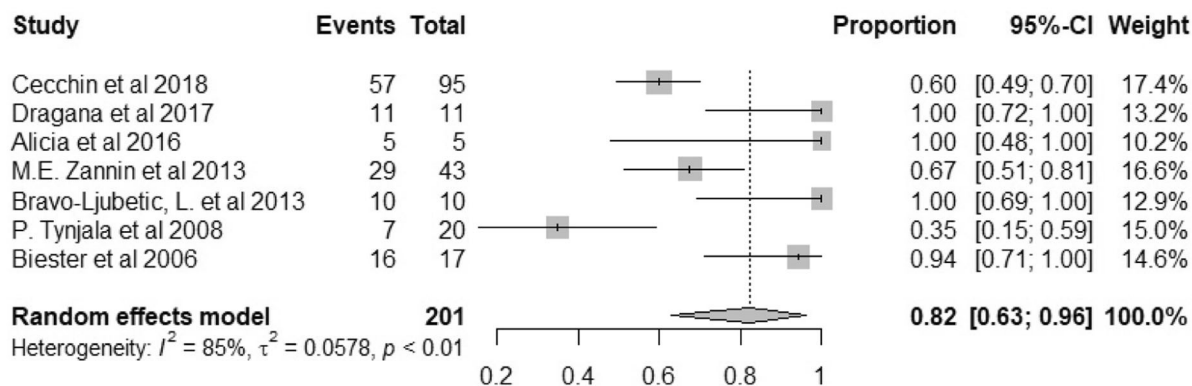| Source	Study type	Patients	Treatment group (no. of participants, F/M)	Control group (no. of participants, F/M)	Age, years	Length of follow-up (months)	Control of intraocular inflammation (TG vs CG)	Visual acuity	Corticosteroid sparing (TG vs CG)	AEs and SAEs (TG vs CG)
Zannin et al. [37]	Prospective cohort study	85	ADA (43, 36/7) Every 2 weeks at a dosage of 1 mg/kg (maximum 40 mg). Refractory to treatment progressively increased to a maximum of 40 mg	IFX (42, 35/13) 5 mg/kg at 0, 2, 6, and 12 weeks and continued every 6–8 weeks; refractory to treatment, shorter intervals (maximum every 4 weeks)	9.7 (4.9 uveitis onset)	12	Clinical remission: the absence of active uveitis for more than 6 months on systemic treatment and with no or minimal topical treatment ADA vs IFX: 29 vs 18	NA	NA	The rate of AEs: 4.7 vs 18.8 per 100 PY ADA: 2 systemic symptoms (urticarial rash, Prolonged menses) IFX: 3 infections, (upper respiratory tract, herpes zoster virus, urinary tract; 3 urinary tracts; 3 systemic symptoms (2 headaches, 1 irritability) No SAEs
Bravo-Ljubetic et al. [24]	Retrospective case series	10	ADA (10, NA) 40 mg in children weighing ≥ 30 kg, 20 mg in children weighing < 30 kg every 2 weeks	NA	9.21	42.4	SUN improved activity: 10	NA	NA	NA
Tynjala et al. [48]	Retrospective case series	20 Seventeen (85%) patients had polyarticular JIA	ADA (20, 16/4) subcutaneously every 2 weeks (40 mg to 18/20 patients and 20 mg to two patients weighting < 30 kg)	NA	13.3	18.7 (4.5–35.6)	SUN improved activity: 7	NA	7/12	AEs: NA Upper respiratory infection 55% Local skin reaction 25% Sinusitis 15% No SAEs

Table 1 continued

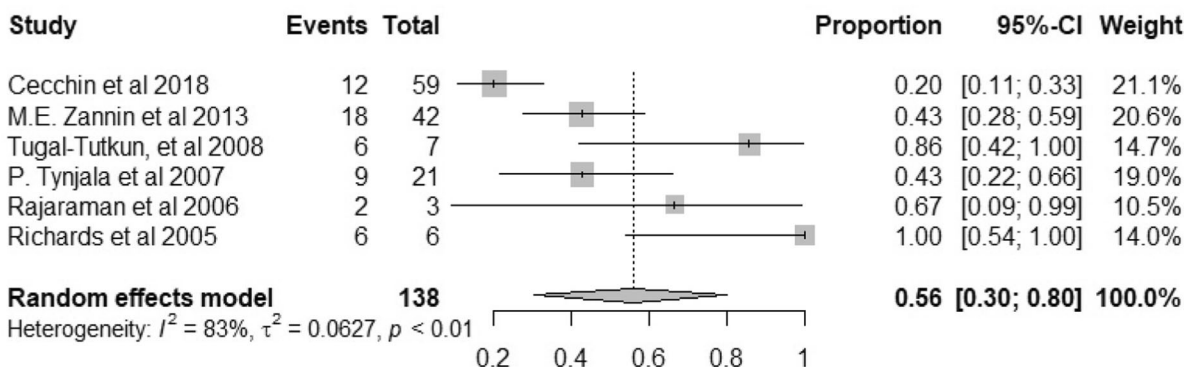| Source	Study type	Patients	Treatment group (no. of participants, F/M)	Control group (no. of participants, F/M)	Age, years	Length of follow-up (months)	Control of intraocular inflammation (TG vs CG)	Visual acuity	Corticosteroid sparing (TG vs CG)	AEs and SAEs (TG vs CG)
Biester et al. [47]	Retrospective case series	17	ADA (17, 14/3) 0–40 mg every two weeks depending on body weight	NA	5.8 (2–19)	16.8	No relapse or more than 2 relapses less than before treatment:16	NA	15/17	AEs:7 Mild local reaction (2) Burning sensations (3) Pain around the injection site (2) SAEs: 1 elevation of liver enzymes
Tugal-Tutkun, et al. [34]	Retrospective case series	7	IFX (7, 4/3) 5 mg/kg 0, 2, and 6, and repeated every 8 weeks	NA	6.8 (4–11)	34	SUN improved activity: 6	Improved 5 Stable 2	3/3	AEs:1 mild infusion reaction and herpes zoster
Tynjala et al. [25]	Retrospective cohort study	45	ETA (24,NA) 0.4 mg/kg twice weekly subcutaneously	IFX (21, NA) 3–6 mg/kg intravenously, initially at 2, 4, and 6-week intervals, and later based On the response every 4–8 weeks	5.6 (1.3–16.9)	24	International Uveitis Study Group standard: 5 vs 9	NA	NA	AEs: NA SAEs 4 vs 3 ETA: pneumonia, unspecified abdominal infection, sight-threatening macular edema, retinal ablation IFX: peritonsillar abscess, pansinusitis, alopecia with highly increased ANA and DNA antibodies
Rajaraman et al. [35]	Retrospective case report	3	IFX (3, 2/1) 5 mg/kg 0, 2, and 6, and repeated every 8 weeks	NA	6.5	14.2	SUN improved activity: 2	Improved 2 Worse 1	1/1	AEs:1 Bronchospastic cough No SAEs

Table 1 continued

Source	Study type	Patients	Treatment group (no. of participants, F/M)	Control group (no. of participants, F/M)	Age, years	Length of follow-up (months)	Control of intraocular inflammation (TG vs CG)	Visual acuity	Corticosteroid sparing (TG vs CG)	AEs and SAEs (TG vs CG)
Richards et al. [51]	Retrospective case series	6	IFX (6, 5/1) 5 and 10 mg/kg at weeks 0, 2, and 4, and thereafter 6–8 weekly	NA	11.6 (7.5–17)	27	SUN improved activity: 6	NA	6/6	AE:2 Itching, sneezing, and rhinorrhea pityriasis versicolor SAE 0
Saeed et al. [32]	Retrospective case series	9	ETA (9, 6/3) subcutaneous injection at a dosage of 0.4 mg/kg (maximum dosage of 25 mg) twice a week	NA	11	NA	SUN improved activity: 6	Worse 2 Stable 7	NA	NA
Smith et al. [36]	Retrospective case series	3	ETA (3, 2/1) 0.4 mg/kg twice weekly by subcutaneously	NA	18.7	12	Decrease cell counts by slit-lamp biomicroscopy: 1	Improved 0 Stable 2 Worse 1	NA	No AEs andSAEs
Palmou-Fontana et al. [52]	Retrospective case series	7	GLM (7, 5/2) 50 mg/every 4 weeks subcutaneously	NA	21.7 ± 7.5	6	Complete remission: 4	BCVA: 0.5 to 0.62 (p = 0.018)	NA	AEs: 2 Local erythema at the injection site
Miserocchi et al. [31]	Retrospective case series	13	GLM (13, 10/3) 50 mg monthly subcutaneously	NA	23.1	22.4	Without uveitis at last visit: 9	Improved 3 Stable 10 Worse 0	5/7	AEs: 2 Pulmonary infection Skin reaction
Sanna Leinonen et al. [53]	Retrospective case report	3	CZP(3,2/1) Every 2 weeks Starting with a loading dose of 400 mg 3 times and continued with a dose of 200 mg	NA	18.6 (15, 24, 17)	11 (9, 10, 14)	SUN improved activity: 3	NA	NA	NA

RCT randomized clinical trials, *DB* double-blinded, *F/M* female/male, *NA* not available, *PY* patient-year, *TG* treatment group, *CG* control group, *AE* adverse event, *SAE* serious adverse event, *logMAR* logarithm of the minimum angle of resolution, *ADA* Adalimumab, *IFX* Infliximab, *ETA* Etanercept, *CZP* Certolizumab pegol, *GLM* Golimumab, *LFP* laser flare photometry, *AC* anterior chamber, *BCVA* best-corrected visual acuity
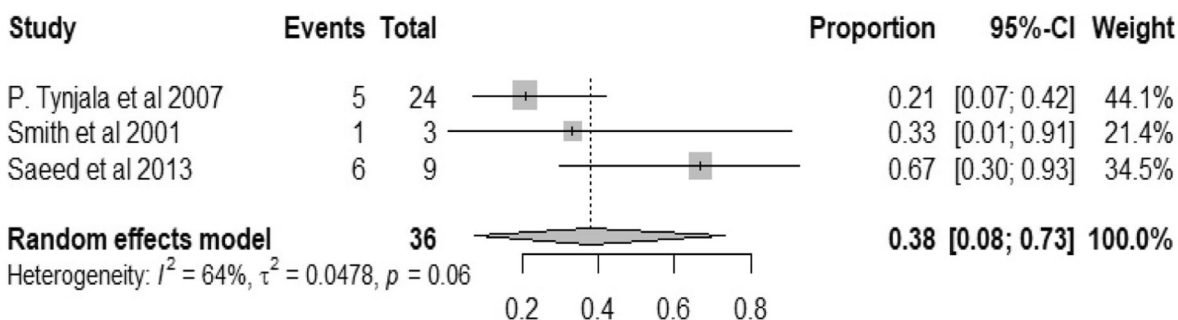
A: The pooled proportion of intraocular inflammation controlled of ADA

Study	Events	Total	Proportion	95%-CI	Weight
Cecchin et al 2018	57	95	0.60	[0.49; 0.70]	17.4%
Dragana et al 2017	11	11	1.00	[0.72; 1.00]	13.2%
Alicia et al 2016	5	5	1.00	[0.48; 1.00]	10.2%
M.E. Zannin et al 2013	29	43	0.67	[0.51; 0.81]	16.6%
Bravo-Ljubetic, L. et al 2013	10	10	1.00	[0.69; 1.00]	12.9%
P. Tynjala et al 2008	7	20	0.35	[0.15; 0.59]	15.0%
Biester et al 2006	16	17	0.94	[0.71; 1.00]	14.6%
Random effects model		201	**0.82**	**[0.63; 0.96]**	**100.0%**

Heterogeneity: $I^2 = 85\%$, $\tau^2 = 0.0578$, $p < 0.01$

B: The pooled proportion of intraocular inflammation controlled of IFX

Study	Events	Total	Proportion	95%-CI	Weight
Cecchin et al 2018	12	59	0.20	[0.11; 0.33]	21.1%
M.E. Zannin et al 2013	18	42	0.43	[0.28; 0.59]	20.6%
Tugal-Tutkun, et al 2008	6	7	0.86	[0.42; 1.00]	14.7%
P. Tynjala et al 2007	9	21	0.43	[0.22; 0.66]	19.0%
Rajaraman et al 2006	2	3	0.67	[0.09; 0.99]	10.5%
Richards et al 2005	6	6	1.00	[0.54; 1.00]	14.0%
Random effects model		138	**0.56**	**[0.30; 0.80]**	**100.0%**

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0627$, $p < 0.01$

C: The pooled proportion of intraocular inflammation controlled of ETA

Study	Events	Total	Proportion	95%-CI	Weight
P. Tynjala et al 2007	5	24	0.21	[0.07; 0.42]	44.1%
Smith et al 2001	1	3	0.33	[0.01; 0.91]	21.4%
Saeed et al 2013	6	9	0.67	[0.30; 0.93]	34.5%
Random effects model		36	**0.38**	**[0.08; 0.73]**	**100.0%**

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.0478$, $p = 0.06$

Fig. 2 Forest plot on the pooled proportion of intraocular inflammation control with the treatment of adalimumab (**a**), infliximab (**b**), etanercept (**c**), respectively. As I^2 statistic showed the obvious heterogeneity of the studies, random-effects model were used to present the pooled results

ADA

IFX

ETA
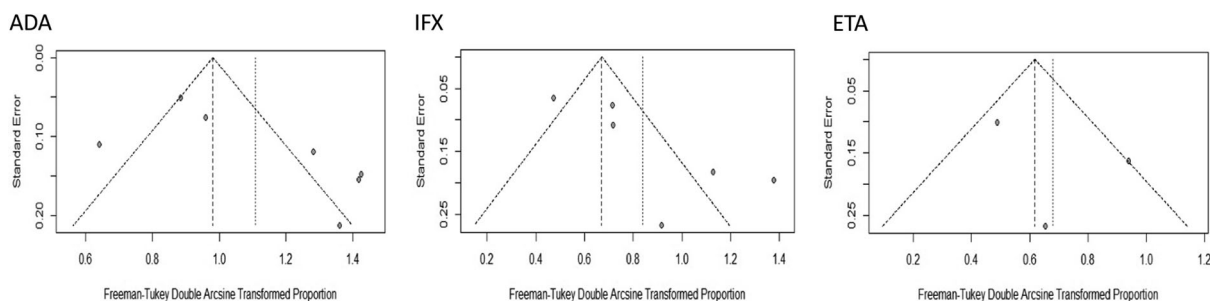
Fig. 3 Funnel plots on intraocular inflammation control in children with JIA-U regarding to adalimumab (ADA), infliximab (IFX), etanercept (ETA)

treatment, in 0 (0%) of 2 patients with ETA treatment, and in 5 (71.4%) of 7 patients with GLM treatment, respectively.

Safety

RCT conducted by Ramanan, et al. [27] indicated that the AE rate of ADA treatment (10.60 per Patient Year (PY), 95% CI 9.77 to 11.44 per PY) was statistically different from that of the control group (7.12 per PY, 95% CI 5.89 to 8.53 per PY) and the most common AEs of ADA were infections and infestations (83%); while the rate of SAEs was low (0.29 per PY). The five SAEs in ADA were cataracts, injection site reactions, glaucoma, arthralgia and arthritis. Two cohort studies [26, 37] comparing ADA and IFX consistently showed that the AE rate of IFX was higher than that of ADA. In the cohort study conducted by P. Tynjala et al. [25], the SAEs were reported in 4/24(16.6%) patients during etanercept treatment and in 3/21 (14.3%) patients taking infliximab. The reported SAEs in ETA were sight-threatening macular edema, retinal ablation, unspecified abdominal infection and pneumonia. As for IFX, the reported SAEs included peritonsillar abscess, pansinusitis and alopecia with highly increased ANA and DNA antibodies. In addition, Eachempati, S.B. et al. [28] reported a rare SAE of IFX, transient acute coronary syndrome and arrhythmias, which reminded us to be wary of sudden chest pain during or after the infusion of IFX. Regarding GLM and CZP, there were no special AEs and SAEs reported according to the

currently availab information. The specific AEs and SAEs are listed in Table 1.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis exploring the efficacy and safety of anti-TNFα therapy in JIA-U treatment. According to the analysis, ADA is the best choice. IFX is better than ETA but without statistical difference. GLM and CZP are effective for JIA-U patients, but more evidence is needed.

JIA-U is still a big challenge for pediatric rheumatologists and ophthalmologists due to its insidious onset, sight-threatening complications and difficulties in treating concomitant articular and ocular symptoms [38]. Patients with oligoarticular JIA and especially positive ANA are more prone to develop refractory uveitis. For them, the arthritis is often treatable with intra-articular corticosteroids and DMARDs, while the refractory uveitis needs timely systemic therapy including biologicals. Other subtypes, such as psoriatic and enthesitis-related JIA, are rarely associated with refractory uveitis, probably because they receive systemic treatment early in the disease course. The key to JIA-U treatment is early detection through regular screening and timely control of disease activity. In children with JIA-U who don't respond to topical glucocorticoids and methotrexate, anti-TNFα therapy is usually added. Either ADA or IFX is recommended over ETA, as ETA is reported to be ineffective and at

Table 2 Differences in the pooled proportion of intraocular inflammation control between adalimumab, infliximab, etanercept

Adalimumab	Infliximab	Etanercept	Chi-square	*P*
82%	56%		26.24	< 0.001
82%		38%	13.43	< 0.001
	56%	38%	0.13	0.71

high risk of new-onset uveitis or flares [25, 29, 39, 40].

In order to systematically evaluate the efficacy and safety of anti-TNFα therapy in patients with JIA-U, we performed a meta-analysis in this study. After a stepwise process of literature selection, three RCTs, twelve case series, three retrospective cohort studies, and three case reports were included. Based on the Cochrane handbook, results from different study designs are expected to differ systematically, leading to increased heterogeneity, therefore, randomized trials and non-randomized studies should not be combined in a meta-analysis. Accordingly, the three RCTs were not included for meta-analysis in this study, and instead carefully reviewed one by one. Their results are also in line with those of the meta-analysis. Significant efficacy was revealed for ADA treatment in two RCTs [27, 28], but not for ETA in another RCT[29]. There is no RCT exploring the efficacy of IFX in the treatment of JIA-U so far. In the meta-analysis, the pooled proportion of CII was 82%, 56% and 38% for ADA, IFX and ETA respectively. ADA is significantly better than IFX and ETA in the control of intra-ocular inflammation, but no statistical difference was found between IFX and ETA. ADA is also better than IFX in improving or stabling VA. In addition, a cohort study [41] showed that uveitis was more likely to remain in remission in those receiving ADA than IFX during 40 months of follow-up. Unlike our results, a meta-analysis conducted in 2014 did not show any significant difference between ADA and IFX in the treatment of childhood autoimmune chronic uveitis [42]. The difference of the two meta-analyses may come from two aspects. One is that our study focused on JIA-U patients but they explored all the childhood autoimmune uveitis.

In addition, after their analysis in 2014, more studies have been performed and more evidence accumulated in recent years. Our results would be closer to the real situation. As for GLM and CZP, although good efficacy have been seen in controlling intraocular inflammation, their efficacy still needs further verification because of the limited number of studies.

As for safety, most reported adverse events of anti-TNFα therapy were tolerable, and some SAEs were reported. The development of malignancy wasn't revealed during the JIA-U treatment, which may be due to a paucity of long-term follow-up studies. The risk of the development of malignancies after anti-TNFα therapy is still inconclusive. Meta-analysis in other diseases showed that the risk of malignancy did not increase in the short-term treatment [43, 44]. However, in the registry of some health authorities, the incidence of lymphoma and melanoma has increased [45]. Clinicians should still bear in mind the risk of the development of malignancies, especially in patients with previous malignancy or premalignant status.

Several limitations have to be considered for this meta-analysis. First, the majority of the studies included are case series. Its inherent low evidence strength makes our conclusion less persuasive. There is an urgent need for high quality studies. Second, the definition of outcome measures was inconsistent. Clinical remission [26, 37], no relapse [46, 47] or SUN improved uveitis [24, 30, 48] were used as outcome measures in different studies, which may lead to obvious heterogeneity. Although the SUN criteria have made a huge contribution to standardizing outcome reporting, many clinical trials still have not reached consensus nowadays [42, 49]. The broad variety of outcome measures

makes the comparison of responses to different treatments quite difficult. Third, the different features of participants in different studies may also lead to the obvious heterogeneity. In order to improve the quality of meta-analysis in the future, more studies with high quality, uniform outcome measures and clear identification of patients are warranted.

CONCLUSION

In conclusion, ADA is better than IFX for JIA-U treatment with respect to its efficacy and safety. The efficacy of IFX is higher than ETA but with no statistical significance. In addition, GLM and CZP may be proxies for ADA but more evidence is needed.

ACKNOWLEDGEMENTS

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