

# Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review

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**Objective:** To summarize updated evidences on the efficacy and safety of adalimumab (ADA) in the treatment of patients with non-infectious uveitis.

**Patients and methods:** A systematic search between January 2000 and September 2017 was conducted using PubMed, Embase, and Cochrane libraries. We investigated control of inflammation, improvement of visual acuity (VA), corticosteroid-sparing effect, and adverse events (AEs) or serious adverse events.

**Results:** Three randomized clinical trials (RCTs) and 20 non-RCTs were included and analyzed. The pooled proportions of inflammation control were 74% (95% CI 64%–82%) and 79% (95% CI 69%–87%) in groups of  $\leq 6$ - and  $\geq 12$ -months follow-up durations. No significant difference was found between the two groups ( $\chi^2 = 0.920$ ,  $p = 0.337$ ). Analysis of subgroups classified by degree of being treatment-naïve for anti-TNF $\alpha$  agents showed the inflammation control reached a high of 87% (95% CI 80%–92%) when subjects were “almost naïve” to anti-TNF $\alpha$  before ADA treatment. VA was improved by three or more lines in 41.3% (52/126) eyes, and was equal to or better than the baseline in 88.8% (142/160) eyes. Corticosteroid sparing was observed in 82.0% (91/111) of the patients; among them, 48.8% (40/82) discontinued use of corticosteroid completely. Minor drug-related adverse events were reported. The treatment effects of ADA were generally consistent in the three RCTs, and ADA reduced the risk of treatment failure by 43%–75%.

**Conclusion:** The current review provided evidences that ADA might be a promising choice in reducing inflammatory activity, gaining VA, and sparing corticosteroid use with minor AEs when applied in treating non-infectious uveitis.

**Keywords:** adalimumab, non-infectious uveitis, anti-TNF  $\alpha$ , uveitis treatment

## Introduction

Non-infectious uveitis, associated with an underlying, systemic, vision-threatening disease, is characterized by inflammation in the uveal tract.<sup>1-3</sup> Currently, the mainstay therapy of uveitis is corticosteroids. However, some types of non-infectious uveitis, especially those that are refractory, do not respond well to corticosteroid treatment. Adalimumab (ADA) is a widely used full-length human monoclonal antibody that targets tumor necrosis factor alpha (TNF $\alpha$ )<sup>4,5</sup> – a pro-inflammatory cytokine involved in intraocular inflammation. Emerging evidences have shown that ADA is moderately or highly efficacious in suppressing uveitis, allowing a significant reduction in the mean immunosuppression load and the mean corticosteroid dose.<sup>6-17</sup> Moreover, some expert consensus statements have recommended ADA as the first-choice anti-TNF agent for the management of uveitis secondary to juvenile idiopathic arthritis (JIA), ankylosing

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spondylitis, and uveitis of diverse etiologies, such as sarcoidosis, Behçet's disease, Vogt–Koyanagi–Harada disease,<sup>18,19</sup> and even as rescue therapy<sup>20</sup> after the failure of other anti-TNF $\alpha$  agents. Although approved for the treatment of non-infectious uveitis in adults in the USA, Japan, and some countries in Europe (EU), worldwide, ADA is still not yet used widely in the treatment of non-infectious uveitis.

We herein undertook a meta-analysis and review aiming at systematically evaluating the efficacy, safety, and tolerability of ADA in the treatment of non-infectious uveitis.

## Patients and methods

### Eligibility criteria

We defined the inclusion criteria as follows: 1) non-infectious autoimmune uveitis-related studies; 2) patients who were on a chronic course under immunosuppressive therapy and systemic steroid treatment previously for at least 3 months and showed refractory uveitis; 3) the uveitis inflammatory activity grading was described according to the Standardization of Uveitis Nomenclature (SUN) working-group criteria;<sup>21</sup> 4) at least a 3-month median follow-up duration; and 5) studies with at least five patients to avoid a positive report bias.

### Outcome measurement

- 1) Control of inflammation was defined by the anterior chamber cells and/or vitreous haze decreasing by two levels or to grade 0.5+ or 0, respectively, according to the SUN criteria and National Eye Institute system criteria adopted by SUN in at least one eye. Besides, some studies require structural complications or comorbidities, such as cystoid macular edema (CME), vasculitis, and papillary edema, to be confirmed by fluorescein angiography (FA) or optical coherence tomography (OCT) examinations. For a comprehensive analysis, we included all of these studies.
- 2) Controlled visual acuity (VA), according to the SUN criteria,<sup>21</sup> was defined as a doubling of the visual angle (converted into logMAR format) in the involved eye from baseline corresponding to three lines on a decimal scale with a logarithmic chart. Further, we collected information of VA maintaining stable or improving at least one line.
- 3) Corticosteroid sparing was defined as a significant decrease, by  $\geq 50\%$ , for example, or cessation of daily corticosteroid use since the day anti-TNF treatment was initiated.
- 4) Time to treatment failure was defined as the time up to when SUN-cell-activity score (anterior chamber cell/vitreous haze grade) had worsened (a two-grade increase)

or had not improved (decrease to  $\leq 0.5+$ ). Studies that adopted multiple endpoints, including increase of vitreous haze/anterior chamber cells and new active lesions and decrease in best-corrected VA (BCVA), were also discussed in our study.

- 5) Safety was assessed by the occurrence of adverse effects (AEs). Serious adverse effects (SAEs) were specified as ADA treatment interruption, hospitalization, or death.

### Search strategy

A relevant literature search was conducted using the electronic databases of Medline, Embase, and the Cochrane Library from January 2000 to September 2017, with language restriction of only articles in English. The terms/key words were “uveitis” or “iridocyclitis” crossed with “anti-TNF  $\alpha$ ” or “anti-tumor necrosis factor alpha” or “anti TNF alpha” or “TNF alpha inhibitors” and “adalimumab”. Uveitis was not restricted by the words of “chronic”, “non-infectious”, and “autoimmune” to enlarge the number of hits in the literature to be screened. Study types were not limited to clinical trials. Thus, uncontrolled case series, nonrandomized, retrospective clinical studies, and prospective open-label trials were also included to provide more evidences related to the effectiveness of ADA in uveitis.

### Study selection and data collection

Two reviewers (Shuai Ming and Kunpeng Xie) screened the titles and abstracts of the searched studies independently to determine their relevance to this study. Full-text articles were assessed for eligibility according to the eligibility criteria. Evaluations of methodological quality and risk of bias were undertaken. Discussions were held resolve any disagreement in the procedure until a consensus was reached. A standard form was applied for information collection from the selected articles. The information captured included: study design type, number of patients, age and gender statistics, duration of follow-up, and definitions of outcomes and results. If the same registered trial appeared on sequential or multiple publications, the data from the most recent or comprehensive publication was included.

### Data synthesis and analysis

An evaluation of outcomes was done per patient, with the exception of VA which was mainly pooled per eye. Description of outcomes was graded dichotomously by “yes” or “no” responses. With different analytical methods, studies reported their outcomes, either based on time points (eg, 3, 6, or 12 months) or based on the median follow-up durations.

For the analysis of the pooled proportion of controlled inflammatory activity, extracted data were categorized into two groups of “6 months or less” and “12 months or more” and this grouping helped explain the short-term and relatively long-term efficacy of ADA on uveitis, respectively.

The strength of evidence of non-randomized clinical trials (RCTs) was rated using a scale from the Scottish Intercollegiate Guideline Network (SIGN).<sup>22</sup> The modified Jadad Scale was used to assess the methodological quality and risk of bias of RCTs. All assessments were independently done by two investigators (Shuai Ming and Kunpeng Xie).

The meta-analysis was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses guidelines, in principle.<sup>23</sup> The pooled proportions (controlled uveitis activity) and 95% CIs were realized by the “Metaprop” program package in R 3.2.0. Study homogeneity was investigated using  $I^2$  statistic to quantify the percentage of variation across studies. A random-effects model (DerSimonian–Laird method) was used to present the pooled results if the  $I^2 > 50\%$  and  $p < 0.1$ . Otherwise, a fixed-effects model (Mantel–Haenszel method) was used. Subgroup analysis was conducted if obvious heterogeneity existed. The difference in groups of pooled proportions was statistically significant when  $p < 0.05$ . A meta-analysis of

clinical trials was done with a similar statistical procedure, if possible; otherwise, a systematic review was conducted.

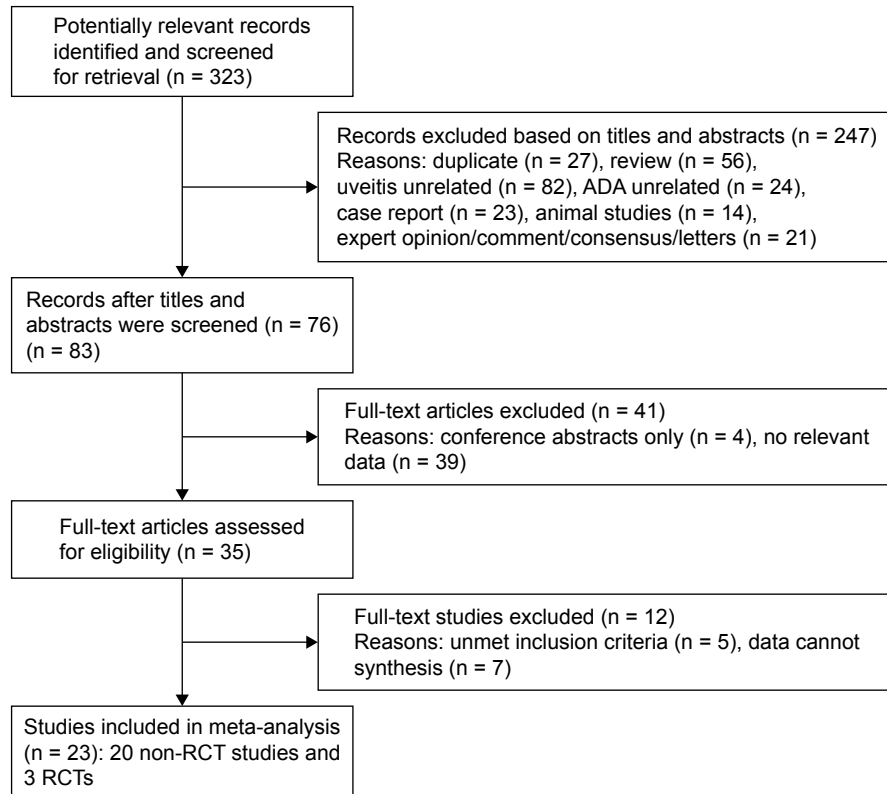
## Results

### Selection of studies

A total of 323 possible relevant articles were returned from a computerized search of various databases; of these, 247 were excluded after scanning the titles and abstracts. After full-text scrutiny of the remaining 76 articles, we included 35 studies which were specific to the research questions and contained useful information. Thereafter, 12 potentially eligible articles were removed because they did not meet our inclusion criteria or their data type could not be synthesized together. Finally, 23 studies were retained for the meta-analysis, with 20 non-RCTs and three RCTs. The systemic procedure and detailed exclusion criteria in each step are shown in Figure 1.

### Characteristics of included studies

Table 1 shows the summary characteristics of the 20 selected non-RCTs studies.<sup>9,10,12,20,24–39</sup> All of these studies were observational, nonrandomized case series from EU or the US. All studies had a median or mean follow-up duration of more than 6 months, with one exception.<sup>12</sup> In all studies, ADA was administered at 40 or 20 mg/m<sup>2</sup> – depending on



**Figure 1** Flow diagram demonstrating the process of study identification. **Abbreviations:** ADA, adalimumab; RCT, randomized clinical trial.

Table 1 Basic characteristics and endpoint outcomes entered for 18 non-RCT studies

Study/ country	Study design	No. of patients (female/ male)	Age, years	Follow-up duration (months)	Naïve prior to ADA	Inflammation prior to control (n/N)	Visual acuity change	Medication tapering	AEs and SAEs	ADA discontinuation	Evidence strength
Cordero-Coma et al <sup>24</sup> /USA	Nonrandomized, prospective observational study	25 (8/17)	41 (3–73)	6	100%	18/25	NA	NA	One AEs discontinued ADA treatment	2/25, one for AEs, another for treatment failure	III
Mercier et al <sup>25</sup> / France	Monocentric observational retrospective study	21 (11/10)	51.4 ± 15.5	NA	100%	6/7 at 6 months, and 4/5 after >12 months	Improved by 0.27 ± 0.34 (logMAR)	Unextractable	Unextractable	1/8 patients with multiple sclerosis attributed to ADA treatment cessation	III
Muñoz-Gallego et al <sup>26</sup> /Spain	Retrospective case series	12 (9/3)	13 (11–16)	Mean: 38.2	100%	12/12	Improved: 6/19 eyes, no absence of any worsening: 17/19 eyes	NA	No treatment related SAEs	3/12, 1 discontinuation for palmoplantar psoriasis, two interruptions of ADA treatment	III
Fotiadou et al <sup>27</sup> /Greece	Case series	5 (3/2)	51 (38–62)	6	75%	5/5	NA	NA	NA	NA	III
Vallier et al <sup>28</sup> / France	Retrospective multicenter study	37 (22/15)	37 (31–46)	Median: 21	100%	23/24	NA	Unextractable	No SAEs. 10/37 patients were found to have AEs due to infections (5/37) and injection-site reactions (3/37)	NA	III
Doycheva et al <sup>29</sup> /Germany	Retrospective case series	31 (19/12)	5 (1–13)	≥24	100%	18/23	NA	Unextractable	Drug-related AEs occurred in 6/28 patients. 2/28 stopped the ADA treatment and chickenpox	2/28 patients stopped ADA for Henoch– Schönlein purpura and chickenpox	III
Simonini et al <sup>30</sup> / Italy	Prospective, case series open-label study	14 (9/5)		≥12	100%	13/14	16/26 eyes improved, 19/26 eyes maintained normal VA	12/14 stopped steroid during 6 months; all responders stopped steroid before completing 1 year of treatment	NA	NA	II+
García-De- Vicuña et al <sup>9</sup> / Spain	Prospective open-label, multicenter study	39 (28/11)	11.5 ± 7.9	≥6	NA	AC and PC grade decrease of 1.6 ± 1.0 and 2.0 ± 2.69, respectively	4/32 eyes improved, 30/32 eyes had absence of any worsening	Unextractable	Only minor AEs	1/32 of patients discontinued the ADA because of uveitis reactivation	

Dobner et al <sup>31/</sup> Austria	Retrospective case series	60 (34/26)	37.3 (4–71)	22 (3–64)	58.30%	38/56	35/59 persons improved (two lines), 5/59 persons had absence of any worsening	Prednisone dose reduced in 28/39 patients; 8/39 remained stable on low doses ( $\leq 7.5$ mg); but, in 3/39, the dose had to be increased	NA	13/60 of patients stopped treatment with ADA. Inefficacy in 8, systemic disease in 3, and worsening of uveitis in 2 patients	III
Bravo-Ljubetic et al <sup>10/</sup> Spain	Monocentric observational retrospective study	14 (12/2)	10 (5–17)	36 (15–58)	100%	12/14	NA	NA	Only minor AEs at the site of ADA injection	4/15, 3 patients had lack of response; 1 patient observed satisfactory clinical course without relapse	III
Suhler et al <sup>12/</sup> USA	Retrospective case series	31 (18/13)	40.9 (20–66)	$\geq 3.5$	87.10%	11/18 at 3.5 months had active uveitis	6/29 cases improved 2 lines; 27/29 cases showed absence of any worsening	9/10 of cases reducing prednisone to <10 mg daily dose, and 6/10 cases were able to stop corticosteroids; the average dose reduction was 90%	No SAEs. The most common AEs were headache, common cold, joint pains, and nausea	2/31 patients stopped the study due to significant AEs (hypoglycemic coma and cerebrovascular accident)	III
Sen et al <sup>32/</sup> UK	Case cohort interventional study	17 (10/7)	10 (0–14)	24 (6–36)	53.80%	11/13 and 8/11 at 3 months and 12 months, respectively	4/19 eyes improved; 14/19 eyes showed absence of any worsening	4/6 patients tapered oral prednisolone use during 3 months; 4/13 patients stopped the topical drops; 8/13 patients reduced the topical steroid eye drops during 12 months	No SAEs. 7/17 patients reported stinging and injection-site reactions	3/17 patients stopped ADA for chest infection, suspected tuberculous meningitis, and inadequate control of uveitis	II+
Martel et al <sup>33/</sup> USA	Retrospective longitudinal case series	12 (10/2)	23.3 (18–31)	Median: 0.94	41.70%	6 months: 6/8; 12 months: 4/7	NA	3/8 patients were able to completely stop corticosteroid treatment	NA	No discontinuations due to AEs	III
Calleja et al <sup>20/</sup> Spain	Nonrandomized intervention study	12 (4/8)	36.2 (14–58)	6	100%	10/12	NA	NA	No major systemic AEs were observed	The overall discontinuation rate was 0.26/PY; 3/12 patients discontinued ADA	II+

(Continued)

Table 1 (Continued)

Study/ country	Study design	No. of patients (female/ male)	Age, years	Follow-up duration (months)	Naïve prior to ADA	Inflammation prior to control (n/N)	Visual acuity change	Medication tapering	AEs and SAEs	ADA discontinuation	Evidence strength
Simonini et al <sup>36/</sup> Italy	Prospective, comparative case series	16 (10/6)	5.4 (2.2–11.4)	12	>75%	12 months: 15/16	19/30 eyes and 12/15 patients had improved VA	13/16 at 6 months treatment; 16/16 before completion of 1-year treatment	No SAEs, 5 pain and discomfort, and 2 local reactions	No discontinuations due to AEs	III
Dhingra et al <sup>37/</sup> UK	Retrospective case series	6 (5/1)	5 (2–33)	Mean: 6	0%	4/6	NA	NA	NA	NA	III
Diaz-Llopis et al <sup>34/</sup> Spain	Prospective pilot study	19 (9/10)	34 (25–54)	12	73.70%	17/19	13/38 eyes improved 2 lines; 37/38 eyes showed absence of any worsening load	19/19 patients were able to reduce at least 50% baseline immunosuppression	Only minor local AEs at injection sites	NA	III
Tynjälä et al <sup>35/</sup> Finland	Prospective patient series	20 (16/4)	14 (6–19)	18.7	5%	7/20	NA	7/20 patients discontinued systemic prednisolone. The mean daily dose decreased from 0.1 mg/kg to 0.03 mg/kg	SAEs were not observed. 30 infections (0.97/PY) were recorded	NA	III
Biester et al <sup>36/</sup> Germany	Prospective study	18 (14/4)	NA	19 (2–37)	50%	14/18	NA	NA	No SAEs	1/18 patients discontinued ADA due to elevation of liver enzymes	III
Vazquez- Cobian et al <sup>37/</sup> USA	Prospective patient series	14 (11/3)	11.5 (4–19)	18.1 ± 2.3	100%	12/14	25/26 eyes absence of any worse	11/14 children decreased the use of topical corticosteroid drops; 4/14 discontinued the drops completely; 2/3 discontinued oral steroids	Pain at the injection site was the only AEs reactions occurred that required discontinuation of ADA	No severe reactions occurred that required discontinuation of ADA	III

**Notes:** Continuous variables are shown as the mean ± SD or median (range).

**Abbreviations:** ADA, adalimumab; AEs, adverse events; SAEs, serious adverse events; FA, fluorescein angiography; VA, visual acuity; AC, anterior chamber; PC, posterior chamber; PY, patient-year; NA, not available.

weight – every 2 weeks by subcutaneous injection. Ten studies<sup>10,20,24–26,28–30,37,38</sup> administered ADA as the absolute first-line anti-TNF $\alpha$  agent, whereas only 11.1% used ADA as first-line therapy in two studies.<sup>35,39</sup> Three studies<sup>20,30,32</sup> had a II<sup>+</sup> evidence strength, and the other 17 studies had III strength according to the SIGN criteria.

Table 2 shows the summary characteristics of the three selected RCTs studies.<sup>40–42</sup> Although the three RCTs adopted the same endpoint (time to treatment failure), it was inappropriate to consolidate the outcomes directly. Firstly, uveitis activity was “inactive” in Quan’s patients. Even between the other two studies, choosing “active” uveitis at baseline, the

**Table 2** Main summary of characteristics of the three selected RCTs

Study	No (ADA/ placebo)	Active or inactive in enrollment	Trial regimen	Outcome definition	Safety and comments	Quality score
Ramanan et al <sup>40</sup>	90 (60/30, 2:1)	Active: anterior chamber grade $\geq$ 1+ during the preceding 12 weeks of therapy	MTX for all with no dose reduction or change, ADA vs placebo	Over a period of two consecutive visits, SUN cell-activity score 1) had a 2-grade increase, or 2) had no change when the entry grade of $\geq$ 3, or 3) had a decrease of 1 grade or no change with development of another ocular coexisting condition, or 4) still presented after 6 months of therapy when the entry grade was 1 or 2, or 5) had the worsening of an existing ocular coexisting condition after 3 months, or 6) the use of ineligible concomitant medications, or 7) the intermittent of trial regimen for 4 weeks cumulatively	ADA group: 58.4 follow-up person-years, 588 events of any AEs, 17 events of serious AEs; placebo group: 15.8 follow-up person-years, 103 events of any AE, 3 events of serious AEs	6
Jaffe et al <sup>42</sup>	217 (110/107, 1:1)	Active: anterior chamber or vitreous haze grade $\geq$ 2+ with preceding $\geq$ 2 weeks of therapy	Prednisone burst for all at Week 0, tapering to 0 by Week 15. ADA vs placebo	1) New inflammatory lesion relative to baseline, or 2) a decrease to $\leq$ 0.5+ at week 6 or a 2-step increase in anterior chamber cell or vitreous haze grade, or 3) worsening of BCVA by $\geq$ 15 letters relative to the best state previously achieved	ADA group: 62.5 follow-up person-years, 657 events of any AEs, 161 events of any AEs related to trial intervention, 18 events of SAEs, 6 events of SAEs related to trial intervention; 13 AEs leading to discontinuation of ADA. Placebo group: 44.3 follow-up person-years, 430 events of any AEs, 55 events of any AEs related to trial intervention, 6 events of SAEs, 3 events of SAEs related to trial intervention; 5 AEs leading to discontinuation of ADA	7
Nguyen et al <sup>41</sup>	225 (114/111, 1:1)	Inactive: anterior chamber cell grade/vitreous haze grade of 0.5+ or less	Prednisone burst for all at Week 0, tapering to 0 by Week 19. ADA vs placebo	1) New active inflammatory chorioretinal or retinal vascular lesions, or 2) worsening of BCVA by $\geq$ 15 letters, or 3) a 2-step increase in anterior chamber cell or vitreous haze grade relative to baseline	ADA group: 94.5 follow-up person-years, 831 events of any AEs, 13 events of SAEs; 11 events of AEs leading to cessation of ADA. Placebo group: 71.0 person-years, 642 events of any AEs, 10 events of SAEs; 7 events of AEs leading to ADA discontinuation	7

**Abbreviations:** RCT, randomized clinical trial; ADA, adalimumab; MTX, methotrexate; SUN, Standardization of Uveitis Nomenclature; BCVA, best-corrected visual acuity; AEs, adverse events; SAEs, serious adverse effects.



definition of “active” was different for the anterior chamber grade (Grade  $\geq 1$  in Jaffe et al<sup>42</sup> vs Grade  $\geq 2$  in Ramanan et al). Nonetheless, Ramanan et al designed the trial regimen as an ADA plus methotrexate (MTX), compared to ADA alone in the other two studies, and adopted different outcome definitions as well.

All three RCTs that were included reported methods of sequence generation and allocation concealment in detail. Furthermore, blinding was at least mentioned in the method description. The mean Jadad score was 6.7 (high quality).

## Control of uveitis activity

A total of 18 studies showed controlled activity matching our criteria, of which four<sup>20,24,27,39</sup> contained information of follow-up time  $\leq 6$  months; 11 studies<sup>10,26,28–31,34–38</sup> contained information of follow-up time  $\geq 12$  months; and four<sup>12,25,32,33</sup> contained both. An additional Study<sup>9</sup> reported mean activity grade change ( $1.6 \pm 1.0$  for AC) before and after application of ADA, but was excluded from further analysis.

Figure 2 shows the pooled proportion results of controlled uveitis activity in a meta-analysis. When the follow-up duration was  $\leq 6$  months, the pooled controlled activity proportion was 74% (95% CI 64%–82%), with no statistically significant difference ( $\chi^2 = 0.920$ ,  $p = 0.337$ ) compared to a follow-up duration of  $\geq 12$  months (79%, 95% CI 69%–87%). With obvious heterogeneity in the combination of proportions with follow-up  $\geq 12$  months ( $I^2 = 57\%$ ,  $p < 0.01$ ), a subgroup analysis was conducted by dividing studies into “almost naïve”, “partly naïve”, and “hardly naïve” according to anti-TNF $\alpha$  agent usage prior to ADA treatment. Figure 3 shows that, when ADA was used as the first-line anti-TNF $\alpha$  agent, the pooled proportion of activity control reached the highest value (87%, 95% CI 80%–92%). The improvement proportion revealed a decreasing trend (Cochran–Armitage Trend Test:  $Z = -5.277$ ,  $p < 0.001$ ) in the three subgroups

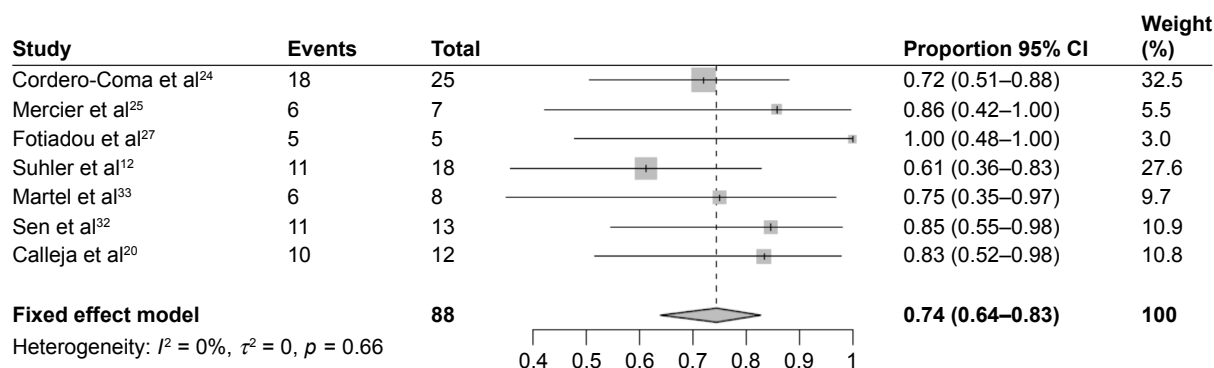
of “almost naïve”, “partly naïve”, and “hardly naïve”. Heterogeneity was well resolved after subgroup analysis.

## Treatment failure

Despite different designs, all three RCTs reported that the time to treatment failure in the ADA groups was two- to three-fold long compared to that in the placebo groups. Patients who received ADA were significantly less likely to have treatment failure than those who received placebo, regardless of whether they were treated concomitantly with MTX. The HR ranging from 0.25 to 0.57 ( $p < 0.05$ ) showed that ADA delayed treatment failure in nearly 50%–75% patients, especially when ADA was used concomitantly with MTX (HR = 0.25). Differing with the other two studies, Nguyen et al<sup>41</sup> reported that, although numerically lower in the ADA group, the treatment-failure risk caused by new lesions and increase in anterior chamber cells/vitreous haze grade did not significantly differ between the ADA and placebo groups (Table 3).

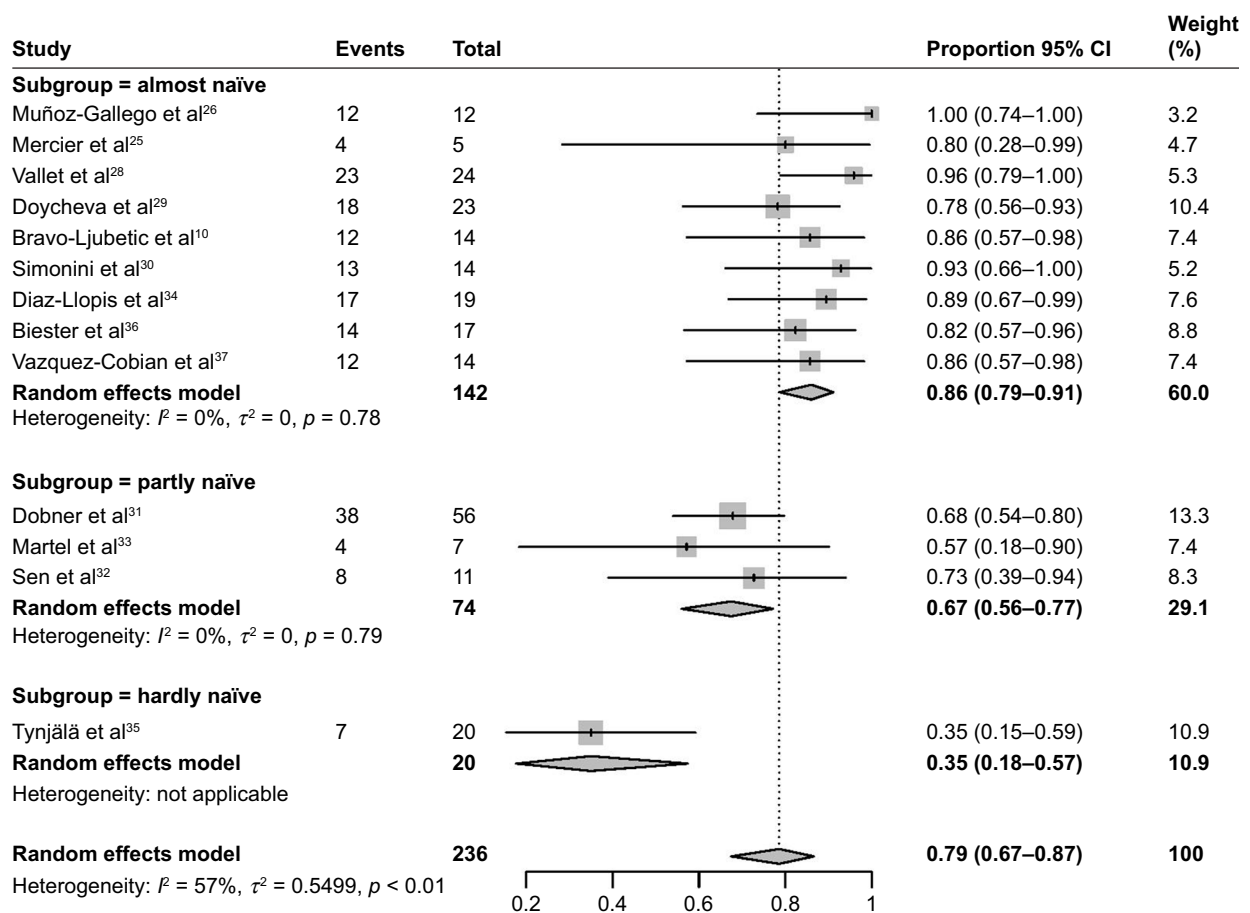
## Visual acuity

A total of 10 studies<sup>9,12,25,26,30–32,34,37,38</sup> reported VA outcomes. Improvement of VA occurred in 52 (41.3%) of 126 eyes, with VA increasing by three or more lines in five studies;<sup>9,26,30,32,38</sup> in 53 (51.5%) of the 103 patients, VA increased by two lines in three studies.<sup>12,31,38</sup> The proportion of VA remaining stable or improving at least one line reached 88.8% (142/160) in the involved eyes<sup>9,26,30,32,34,37</sup> and in 94.3% (83/88)<sup>12,31</sup> of the patients. VA worsened in 11.2% of the eyes and 5.7% of the patients during ADA treatment. Mercier et al<sup>25</sup> reported significantly improved VA by a logMAR decrease ( $0.27 \pm 0.34$ ) on ADA treatment. When determined by worsening VA, RCTs<sup>41,42</sup> showed that ADA treatment could reduce treatment failure by 43%–67%.



**Figure 2** The pooled proportion of uveitis activity control with a follow-up duration of  $\leq 6$  months.





**Figure 3** The pooled proportion of controlled uveitis activity and subgroup analysis when the follow-up duration  $\geq 12$  months. “Almost naïve” means patients were mainly (>70%) anti-TNF $\alpha$  naïve before ADA treatment; partly naïve means half (50%  $\pm$  10%) of the patients were anti-TNF $\alpha$  naïve; hardly naïve means less than 30% of patients were anti-TNF $\alpha$  naïve. Heterogeneity disappeared when analyzed by subgroups.

**Abbreviation:** ADA, adalimumab.

### Corticosteroid sparing

Information on corticosteroid sparing was extractable in nine of the 20 non-RCT articles. Forty (48.8%) of the 82 patients<sup>12,30,32,33,35,37</sup> with ADA treatment completely discontinued corticosteroid, indicating a moderate improvement

in the corticosteroid-sparing effect. Six studies<sup>12,31,32,34,37,38</sup> reported tapering of corticosteroid administration in 91 (82.0%) of the 111 patients. A quantitative analysis<sup>12</sup> showed that the average dose was reduced by 90% (from 31 to 3 mg) from the pretreatment visit to the end of ADA medication.

**Table 3** Summary of ADA efficacy on the treatment of non-infectious uveitis in three selected RCTs

Study	Endpoint & components	Time to treatment failure (ADA vs placebo)	HR (95% CI)	p-value
Ramanan et al <sup>40</sup>	Total effect	> 18 vs 6.0 months	0.25 (0.12–0.49)	<0.001
	Anterior chamber cells		0.25 (0.12–0.49)	<0.001
Jeff J et al <sup>42</sup>	Total effect	6 vs 3.3 months	0.50 (0.36–0.70)	<0.001
	Vitreous haze		0.32 (0.18–0.58)	<0.001
	New lesions		0.38 (0.21–0.69)	0.001
	Anterior chamber cells		0.51 (0.3–0.86)	0.010
	BCVA		0.56 (0.32–0.98)	0.040
Nguyen et al <sup>41</sup>	Total effect	> 18 vs 8.3 months	0.57 (0.39–0.84)	0.004
	Vitreous haze		0.79 (0.34–1.18)	0.589
	New lesions		0.55 (0.26–1.15)	0.105
	Anterior chamber cells		0.70 (0.42–1.18)	0.180
	BCVA		0.33 (0.16–0.70)	0.002

**Abbreviations:** RCT, randomized clinical trial; ADA, adalimumab; BCVA, best-corrected visual acuity.

Similarly, García-De-Vicuña et al<sup>9</sup> found that the mean daily dose of prednisolone was successfully decreased from 0.1 mg/kg to 0.03 mg/kg. Details are shown in Table 2.

## Safety

A total of 14 case-series studies and three RCTs had safety information on ADA treatment. According to the available case-series data, 30 patients (30.6%) experienced AEs.<sup>6,29,32,38</sup> However, 12 of the case series explicitly reported that only minor drug-related AEs were observed. In the three RCTs, the incidence of AEs per patient-year was 9.6 events (2,076 events in 215.4 follow-up patient-years). The corresponding incidence of SAEs was 0.22 events (48 events in the same follow-up years). The incidences of both AE and SAEs were numerically higher than those in the placebo groups (9.0 events and 0.14 events per patient-year, corresponding to 1,175 events and 19 events in 131.1 patient-years, respectively). Jaffe et al<sup>42</sup> reported that the incidences of ADA treatment-related AEs and SAEs were 2.6 and 0.1 events per patient-year, respectively. The most frequently reported AEs were injection-site reactions and allergic reactions.

## Discontinuation of ADA

Discontinuation of ADA was reported in 14 case-series studies and two RCTs. In 11 case-series studies, ADA treatment was discontinued in 32 patients (11.6%),<sup>9,10,12,20,24–26,29,31–33,36–38</sup> of which 16 patients (6.2%) discontinued ADA for uncontrolled or worsening of uveitis activity and six (2.3%) discontinued because of AEs. In the two RCTs,<sup>41,42</sup> the incidence of AEs that induced ADA discontinuation was 0.15 events per patient-year (24 events in 157.0 follow-up patient-years).

## Discussion

In our study, many aspects of the efficacy of ADA in uveitis were systematically reviewed including control of inflammation, improvement of VA, and AEs. The presented evidences were collected from RCTs and non-RCTs with different evidence strengths to provide more comprehensive analysis.

We categorized endpoints, for the first time, to two subgroups according to follow-up duration ( $\leq 6$  and  $\geq 12$  months) to examine the short-term and relatively long-term efficacy on inflammation control. The inflammatory activity of uveitis was found to have improved by 74% and 79% in our combined analysis of short- and relatively long-term follow-up periods, respectively, which suggested that a stable efficacy can be achieved. In the  $\geq 12$ -month group, a subgroup of anti-TNF $\alpha$ -naïve patients showed 86% improvement in uveitis activity with ADA treatment.

Furthermore, Simonini et al<sup>43</sup> published a long-period follow-up ( $\geq 12$  months) efficacy of ADA in childhood chronic JIA uveitis which was anti-TNF $\alpha$  naïve. Their result of 87% was consistent with our results ( $p = 0.884$ ). Comparatively, our study contained data from more studies, larger sample size (142 vs 31), wider range of age, and broader diversity of uveitis and, therefore, might have a better population representation. Additionally, we found that being naïve to anti-TNF $\alpha$  agents might affect the efficacy of ADA. The results supported the recommendation of ADA as the first-line choice for corticosteroid-sparing therapy for several types of uveitis.<sup>44</sup> Another review,<sup>45</sup> extracting a small number of cases, reported that ADA was effective with an accumulated crude response rate of 70.6% (24/34), even when used after a previous course of anti-TNF $\alpha$  agents that failed to maintain remission in pediatric autoimmune chronic uveitis. However, in our analysis of all ages, a lower efficacy was found when ADA was used or partly used after treatment with another anti-TNF $\alpha$  agent. In a JIA-associated refractory uveitis cohort,<sup>35</sup> improved ADA activity was found in 35% of patients. Patients with favorable responses were younger at the baseline. Further studies or analysis are still needed to illustrate this difference.

Besides effectiveness in achieving improvement in the eyes with active uveitis, several promising results have contributed to the reasonable use of ADA in clinical treatment. 1) ADA can effectively control the worsening of VA (88.8% involved eyes in our analysis). One third of eyes received VA improvement according to the SUN standard criteria.<sup>21</sup> Structural damage that was already present before ADA therapy might be one reason for the decrease in VA in some eyes.<sup>26</sup> 2) Good corticosteroid-sparing effect. An average of three quarters of the patients significantly reduced corticosteroid use, and nearly half of the patients successfully discontinued corticosteroid use during ADA treatment. Such an effect avoided AEs induced by corticosteroids during uveitis activity control. 3) ADA was generally well tolerated in the treatment of non-infectious uveitis. Most real-world studies only observed minor drug-related AEs. The observed AE profiles were similar to the known safety aspects of ADA use.

Considering the complexity of outcome reporting in the literature, we chose improvement in inflammatory activity as the primary and compulsive outcome. Zannin et al<sup>17</sup> reported the 1-year follow-up of a large cohort of 43 JIA-uveitis patients treated with ADA and similarly concluded that ADA was effective, with a remission rate of 67.4%. We excluded the study because “remission”, defined as absence of active

uveitis for more than 6 months on systemic treatment, was different from our primary outcome. Díaz-Llopis et al<sup>46</sup> found a marked decrease of anterior chamber degree from 1.51 to 0.25 after ADA treatment in 131 uveitis patients. Similarly, another case series<sup>9</sup> with 39 JIA-uveitis children found the anterior chamber degree to have decreased significantly from 2.02 to 0.42. We excluded them because a dichotomous outcome was not extractable.

ADA's efficacy in the treatment of uveitis pooled by case series might appear less persuasive because of an inherent low evidence strength. However, an expert panel recommendation<sup>44</sup> was published in 2014 and accepted ADA as the first- or second-line immunomodulatory agent in treating uveitis based on evidence from case studies. The three RCT studies,<sup>40–42</sup> although a limited number, further confirmed such an efficacy that indicated ADA delayed the time of treatment failure few-fold and greatly reduced the risk of disease recurrence as compared to placebo. Conservatively speaking, because of the unique characteristics of uveitis, many facets of clinical data still have not reached consensus.<sup>44</sup> More high-quality, large-scale RCTs designed with uniform inclusion criteria and recognized endpoints are required.

## Limitations

First, some included studies<sup>24–31</sup> had various uveitis etiologies such as JIA, Behçet's disease, and HLA-B27-associated uveitis. Subgroup analysis according to underlying disease was not conducted because the data were unextractable. Clinical physicians might be interested in ADA efficacy for uveitis of different etiologies. Second, the proportion of VA improvement, ADA discontinuation, corticosteroid sparing, and observed AEs were simply analyzed by averages without considering the weight of each study. In view of the fact that most studies used for analysis only had evidence strengths of SIGN levels II and III, a dialectic point of view is still needed when referring to these results.

## Conclusion

This systematic review and meta-analysis revealed the overall efficacy of ADA in treating non-infectious uveitis and found it was well received for its potent control of inflammatory activity in short- and long-term follow-up durations, moderately high VA improvement, relatively low AE/SAEs, and good corticosteroid-sparing effect. The efficacy was positively determined by RCTs. More high-quality, large-scale clinical trials with similar design are needed to further prove the conclusion with stronger evidence.

## Acknowledgments

This study is supported by the National Natural Science Foundation of China (grant nos. 81470621 and 81770949), Henan Science and Technology Bureau (grant no. 182102310145), National Key Clinical Specialties Construction Program of China, and Henan Key Laboratory of Ophthalmology and Visual Science.

## Author contributions

Shuai Ming: data collection, analysis, manuscript writing. Bo Lei: protocol/project development, paper revising. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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