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SYSTEMATIC REVIEW

Efficacy and safety of biological therapy compared to synthetic immunomodulatory drugs or placebo in the treatment of Behçet's disease associated uveitis: a systematic review

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Abstract

The aim of this study is to compare the efficacy and safety of biological therapy with cyclosporin A (CsA), azathioprine (AZA), or placebo in uveitis flares and other ocular outcomes in patients with Behçet disease. A comprehensive and sensitive search in MEDLINE, EMBASE, and the Cochrane Library was performed. We selected articles including: (1) adult patients with Behçet's and uveitis; (2) on biological therapies; (3) placebo or active control with CsA or AZA; (4) analyzing efficacy (number of uveitis flares, macular edema, etc.) and/or safety outcomes. Meta-analyses, systematic reviews, clinical trials, and observational studies with > 10 patients were included. The selection, data collection and quality assessment (Oxford scale) was carried out by 2 reviewers independently. Nine articles of moderate quality were included (6 randomized clinical trials and 3 retrospective studies) involving 378 patients. Most of them, apart from the study drugs received systemic corticosteroids and other immunosuppressant drugs. Infliximab was more effective than CsA in reducing short-term uveitis flares and severe complications of retinal vasculitis in the long term. Rituximab was similar to a combination of cytotoxic drugs in improving inflammatory activity. In patients with active uveitis adalimumab was associated with a lower risk of uveitic flare or visual impairment, and in patients with inactive uveitis to a significantly lowered the risk of flare upon corticosteroid withdrawal. Secukinumab and daclizumab were not superior to placebo in reducing uveitis flares, like interferonα compared to other drugs. Our results highlight the need for better designed comparative studies on Behçet's uveitis.

Keywords Systematic literature review · Uveitis · Biologic therapy · Behçet's disease

Introduction

Behçet's disease is an idiopathic systemic disorder, classified as vasculitis, and characterized by the presence of recurrent oral and genital ulcers, cutaneous, vascular lesions, central nervous system and ocular impairment [1]. The prevalence of ophthalmologic manifestations in Behçet's disease, including uveitis varies between 50 and 70% of patients and sometimes is associated with potentially severe complications, including blindness. For this reason, it is important to start treatment immediately [2–4].

Topical treatments such as corticosteroids help decrease the severity and duration of uveitic lesions and sometimes can be used without the need of continuous systemic treatments in patients whose recurrences are infrequent and do not cause much discomfort. Systemic treatment modalities are used when it is necessary to prevent recurrences of serious cases [5]. According to the 2018 update of the EULAR recommendations for the management of Behçet's syndrome, patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab (IFX) or interferon α. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment. And, in case of isolated anterior uveitis, systemic immunosuppressives could be considered for those

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with poor prognostic factors such as young age, male sex and early disease onset [6].

Posterior uveitis is a potential serious condition that is managed with immunosuppressive agents such as azathioprine (AZA), cyclosporin (CsA), and together with corticosteroids [7, 8]. These drugs have improved the prognosis of the uveitis, reducing visual loss and resulting sequelae. However, there are refractory cases [2, 9, 10]. With the use of biological therapy, such as IFX and adalimumab (ADA), ocular prognosis has improved definitively [11–14]. There are also some case studies with other anti-TNFα or other biological drugs [15]. However, there are very few well-designed studies with a control group evaluating the efficacy and safety of different biological treatments.

Based on the exposed above, the objective of this work was to analyze, through a systematic literature review, the efficacy and safety of biological therapy compared to CsA, azathioprine (AZA), or placebo in reducing the number of recurrences of uveitis, and in improving visual prognosis in patients with Behcet's disease associated uveitis.

Methods

Study design

A systematic literature review was conducted to identify all studies published up to August 2017 providing information on the efficacy and safety of biological therapy compared to CsA, AZA or placebo in the treatment of uveitis associated with Behçet's disease. This review was carried out following the PRISMA statement. A panel of experts developed the research question and then it was transformed according to the PICO system (patient, intervention, comparison, and outcome).

Search strategy

An expert documentalist (MG) designed a search strategy in the following biomedical databases: MEDLINE (PubMed) (from 1 January 1950 to 22 August, 2017), EMBASE (from 1980 to 22 August, 2017), and the Cochrane Library (Wiley Online) (until August 22, 2017). Initially, the key terms of natural language search were identified and evaluated based on the question in PICO format, and a generic search strategy was then developed, consisting of controlled vocabulary (Medical Subject Headings-MeSH, Emtree and other thesauri) and free language. Later, adjustments were performed by redefining the most relevant terms. The strategy was complemented with field identifiers, truncators, proximity and Boolean operators. This strategy was adapted to the selected biomedical databases. Searches were restricted to the following languages: English, French, and Spanish, but no date or geographical limits were applied. Then, we also searched in the clinicaltrials.gov [16] and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization [17]. Finally, a manual search was performed using the references of the articles that were included and on the summaries of the EULAR conferences 2014–2015–2016 and ACR 2014–2015. Details of the search strategy can be found in the supplementary material.

Inclusion criteria

The studies retrieved by the search strategies were included if they fulfilled the following pre-established criteria: (1) adult patients with Behçet's disease associated uveitis; (2) on treatment with biological therapies defined as those drugs that were developed to be directed highly specifically at particular well-defined molecules expressed on cells or secreted into the extracellular space [18]; (3) treatment with CsA, AZA or placebo, (4) outcome measures to evaluate the efficacy such as rate of uveitis flares, visual acuity (VA), posterior synechiae, macular thickness, blood-to-water barrier permeability, retinal vasculitis, and/or safety (infections, tumors, etc). Meta-analysis, systematic literature reviews, randomized controlled trials (RCTs), open clinical trials, cohort studies, and other observational studies with a comparison and at least 10 patients included.

Selection of studies and data collection

EndNote X7® software was used to manage records retrieved from the searches supplemented with other manual search methods. Two reviewers (TCI and VV) independently performed the selection of the articles following the inclusion criteria. First, the articles were selected by title and abstract and later by full-text reading. In case of disagreement in either of the two phases of selection, it was resolved by consensus with one of the experts. One reviewer (TCI) collected the information from the included studies using standardized forms. When the data were not provided in the text, they were extracted from the tables and figures to obtain the necessary information.

Assessment of methodological quality and data analysis

To assess the methodological quality of the studies, the Oxford scale of evidence levels (see supplementary material) was used. Due to the scarcity of studies and their design, we focused on the description of the studies in evidence tables, results, and in qualitative synthesis instead of meta-analysis.

Results

The search for literature produced 256 articles, of which 18 were read in detail. We identified 12 more articles by manual search. Finally, nine studies met the inclusion criteria. The flow chart in depicted in Fig. 1. The characteristics of the included studies are described in the table of evidence (Table 1), the results in Table 2, and the excluded studies and exclusion reasons are shown in the supplementary data.

We included 6 RCTs and 3 observational retrospective studies in which 378 patients were evaluated, most of whom were middle aged male patients (39–88%) [19–27]. Regarding to treatments, the observational studies compared IFX vs CsA, interferon (IFN) vs CsA + AZA or MTX and IFNα2a vs AZA + CsA [19–21], and the RCTs compared ADA with placebo [22, 23], rituximab (RTX) + MTX vs AZA + cyclophosphamide (CFM) + MTX (combination of cytotoxics, CC) [27], secukinumab (SEC) with placebo [24], daclizumab (DAC) vs placebo [25] and pegIFNα2b with systemic immunosuppressive agents [26]. Doses and regimens were variable (see Table 1). Most of patients also received systemic corticosteroids and other immunosuppressant drugs such as CsA, MTX, AZA, MFN or tacrolimus. The follow-up range was 6–36 months and adverse events (AE) were recorded as a secondary outcome measure in the 9 studies.

Visual acuity

All but one included studies evaluated the change in the VA (using different systems) [19–25, 27]. At 6 months, in the IFX vs CsA study, there were no significant differences in VA improvement (97% vs. 93%) [19]. Similar results were reported when RTX + MTX group was compared with CFM + AZA + MTX ($p = 0.49$) [27], and in the two SEC regimens vs placebo [24]. In other study [20], the VA improvement at 24 months of IFX was superior to the combination of CsA with AZA or MTX ($p < 0.050$), and win one of them, not in the other ($p < 0.05$) [22, 23]. No differences were reported between DAC and placebo in the change of VA [25]. Finally, in another observational study at 36 months, patients treated with IFNα2a improved the VA (≥ 2 lines) in 6 eyes (18.7%), and remained stable (± 1 line) in 21 eyes (65.6%) [21].

Uveitis flares

This outcome was evaluated in 6 of the studies [19–21, 24, 25, 27], and other analyzed ocular flares [26]. One of the studies showed that at 6 months, IFX reported less flares than CsA 0.4 ± 1 vs 1.2 ± 1.2 ($p < 0.05$) [19]. Other

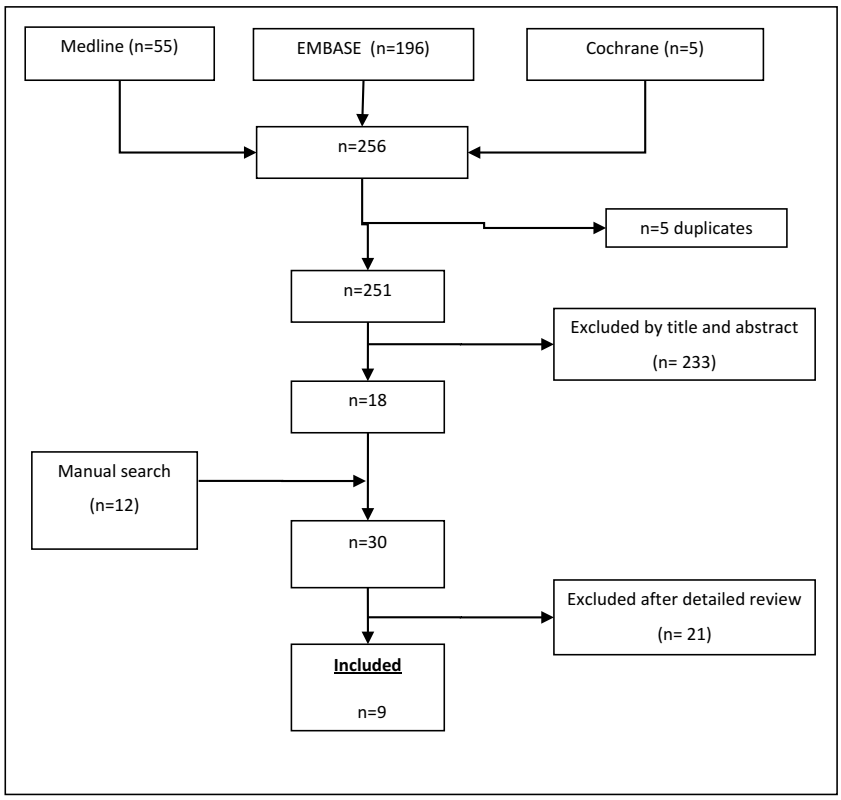

Fig. 1 Studies flow chart

Table 1 Evidence table

#	Study	Population	Intervention	Outcome measures	Quality, comments
1	Yamada et al. [19] observational retrospective, follow-up 12 m	$n=37$ CsA group ($n=20$), 85% men, age (28–63 year) IFX ($n=17$), 88% men, age (25–63 year), CsA ± systemic corticosteroid previous IC: BD (investigation committee criteria) + recurrent uveitis	CsA 3–5 mg/kg/d IFX 5–10 mg/kg iv at 0, 2, 6 w → every 8 w	Best VA Uveitis flares Safety	Oxford 4 No lost to follow-up
2	Tabbara et al. [20] observational retrospective, mean follow-up in the CT group 36 m (24–72 m), in the IFX group 30 m (24–72 m)	$n=43$ CT group ($n=33$), age (14–37 year) IFX group ($n=10$) age (16–35 year), refractory to prednisone, CsA, AZA or MTX IC: BD who meet the following 4 criteria: retinal vasculitis, canker sores, genital sores and skin lesion EC: irreversible ocular disease	CT prednisone 1 mg/kg/d until remission + CsA 2–3 mg/kg/d + AZA 100–150 mg/d or MTX 15 mg/w. If relapse the initial prednisone dose was started IFX 5 mg/kg iv at 0, 2, 4, 6, 8 and 10 w → AZA 1 mg/kg/d. If relapse, IFX 5 mg/kg iv every 2 w for 6 w Co-medications: both groups prednisone as maintenance therapy	VA at 24 m Uveitis flares at 24 m Mean remission time Retinal vasculitis flares at 24 m Complications at 24 m Safety at 24 m	Oxford 4 No lost to follow-up
3	Jaffe et al. [22] double-blind, placebo controlled, RCT, follow-up 80 w or treatment failure	$n=217$ (16 with BD) Placebo group ($n=107$, 4 with BD), mean age 42 yr ADA group ($n=110$, 12 with BD), 43% men, mean age 42 yr IC: non-infectious and active intermediate, posterior uveitis or panuveitis	Placebo ADA 80 mg sc 0 w → 40 mg/2 w Co-medications: both groups prednisone 60 mg/d, ↓ according to protocol and stopped in w 15	Treatment failure at w 6 Risk of treatment failure Δ Anterior chamber cells (0–4+) Δ VH (0–4+) Δ Best VA Median time to macular edema (OCT) Δ Central retinal thickness Δ VFQ-25 and subscores Immunogenicity Safety	Oxford 1b Lost to follow-up: 13.9%
4	Nguyen et al. [23] double-blind, placebo-controlled, RCT, median follow-up 155 d in the placebo group, 245 d in the ADA group	$n=226$ (16 with BD) Placebo group ($n=111$, 6 with BD), 35% men, mean age 42 yr ADA group ($n=115$, 10 with BD), 43% men, mean age 42 yr IC: non-infectious and inactive intermediate, posterior uveitis or panuveitis EC: >1 immunosuppressant within 28 d prior to baseline or opacity that prevents visualization of the fundus	Placebo ADA 80 mg 0 w → 40 mg/2 w Co-medications: both groups prednisone 10–35 mg/d, which was reduced according to protocol and stopped in w 19 Treatment with synthetic immunosuppressants: AZA 6.2%, CsA 11.5%, MTX 14.6%, MFN 15%	Time to treatment failure Treatment failure Risk of treatment failure Δ Anterior chamber cells (0–4+) Δ VH (0–4+) Δ Best VA Median time to macular edema Δ Central retinal thickness Δ VFQ-25 and subscores Immunogenicity Safety	Oxford 1b Lost to follow-up: 14.4%

Table 1 (continued)

#	Study	Population	Intervention	Outcome measures	Quality, comments
5	Davatchi et al. [27] single-blind, RCT, follow-up 6 m	$n=20$ RTX group ($n=10$), 60% men, mean age 29 year CC group ($n=10$), 70% men, mean age 31 yr IC = BD (international criteria) + chronic ocular illness + partial response to combined cytotoxic drugs and corticosteroids	RTX: 1 gr iv 0–15 d + MTX 15 mg/w + prednisolone 0.5 mg/kg/d CC: CFM 1gr/m + AZA 2–3 mg/kg/d + MTX 15 mg/w + prednisolone 0.5 mg/kg/d In both groups, prednisolone was ↓ before ocular inflammation disappeared	VA Posterior uveitis Retinal vasculitis Retinal disc and macular edema TADAI TIAI Safety	Oxford 3b Lost to follow-up: $n=1$ on RTX
6	Buggage et al. [25], double-blind, placebo-controlled, RCT, median follow-up 15 m (1–34 m)	$n=17$ DAC group ($n=9$), 44% men, mean age 33 yr Placebo group ($n=8$), 50% men, mean age 33 year IC: BD (Japanese BD Research Committee criteria) + ≥ 2 ocular flares involving posterior segment requiring systemic treatment for ≥ 3 m EC: relevant comorbidity, end-stage ocular disease	DAC: 1 mg/kg iv every 2 w for 6 m → every 4 w Placebo Co-treatment: prednisone first 6 m → tapering considered if no inflammation If flares or ↑ inflammation: periocular corticosteroids or ↑ doses or addition of a systemic drug	Δ Best VA Uveitis flares Time to uveitis flare Uveitis flare severity Immunosuppressive drugs tapering Safety	-Oxford 2b -Lost to follow-up: n = 2 on DAC group
7	Dick et al. [24], double-blind, placebo-controlled, RCTs (SHIELD trial), follow-up 24 w	$n=118$ SEC 1 ($n=39$), 69% men, mean age 36 yr SEC 2 ($n=40$), 72% men, mean age 34 yr Placebo group ($n=39$), 61% men, age 32 year IC: BD with active or quiescent intermediate uveitis, posterior uveitis or panuveitis + ≥ 2 relapses requiring systemic therapy	SEC 1: 300 mg sc w 0, 1, 2 → every 2 w SEC 2: 300 mg sc w 0, 1, 2 → every 4 w Placebo Co-treatment: corticosteroids and immunosuppressive drugs that were ↓ every 1–2 w unless recurrent flares (tapering stopped + rescue therapy)	Δ Best VA Uveitis flares Time to first uveitis flare Δ ISM score [based on sum of all doses in mg/kg/d or in mg/kg/w) Δ VH score [0–4+) Safety	Oxford 2a Lost to follow-up: $n=7$ SEC 1; $n=9$ SEC 2; $n=5$ placebo $n=5$
8	Lightman et al. [26], single-blind, RCT, follow-up 3 year	$n=72$ PegIFNα2b group ($n=36$): 15 with ocular involvement, 18 with systemic involvement and 3 with both, 39% men, mean age 40 yr No-IFN group ($n=36$): 21 with ocular involvement, 14 with systemic involvement and 1 with both, 44% men, mean age 42 yr IC: BD (International Study Group), requiring systemic corticosteroids and/or immunosuppressants	PegIFNα2b 0.3 μg/kg/w for 26 w + systemic corticosteroids and/or immunosuppressants No-IFN group: systemic corticosteroids and/or immunosuppressants Immunosuppressant drugs: AZA, MMF, CsA, tacrolimus and MTX. Biological treatment was added according to the researcher's criteria	n [%) Ocular flares and severity in patients with ocular disease and systemic disease at 1 and 3 yr Δ Corticosteroids in patients with them at baseline at 1 and 3 year Δ nº immunosuppressive drugs % Requiring biologicals in yr 1 and 3 -Safety	Oxford 2b Lost to follow-up: 30.5%

Table 1 (continued)

#	Study	Population	Intervention	Outcome measures	Quality, comments
9	Hasanreisoglu et al. [21] observational retrospective, mean follow-up CT group 18.2 m (3–48), IFNα2a group 24.75 m (4–88)	$n = 39$ CT group ($n = 23$): 78% men, mean age 29 yr IFNα2a group ($n = 16$): 56% men, mean age 27 yr IC: BD (International Study Group) and severe uveitis treated with CT or IFNα2a for ≥ 3 m	CT: AZA 2–3 mg/kg/d + CsA 3–5 mg/kg/d IFNα2a: 4.5 × 106 IU/d sc In both groups, corticosteroids If posterior uveitis flare, subtenonian injections of triamcinolone permitted	Δ Best VA Uveitis flares per yr Safety	Oxford 4

Main characteristics of the included studies

BD Behçet's disease, *CT* conventional treatment, *CC* combination of cytotoxic drugs, *AZA* azathioprine, *CFM* cyclophosphamide, *IC* inclusion criteria, *EC* exclusion criteria, *CsA* cyclosporine A, *DAC* daclizumab, *IFN* interferon, *IFX* infliximab, *IL* interleukin, *iv* intravenous, *kg* kilogram, *gr* gram, *m* month, *yr* year, *d* day, *mg* milligram, *MFN* mycophenolate mofetil, *MTX* methotrexate, *OCT* optical coherence tomography, *WHO* World Health Organization, *pegIFNα2b* peginterferon α2b, *RCT* randomized controlled trial, *RTX* rituximab; *sc* subcutaneous, *SEC* secukinumab, *TADAI* total index adjusted to the activity of the disease, *TIAI* total index of inflammatory activity, *VFQ 25* visual function questionnaire, *VA* visual acuity, *VH* vitreous haze, *w* week, *ISM* concomitant medication use composite score

reported that uveitis flares at 24 months was 6.3 (4–7) in the conventional therapy group compared with 1.2 (0–4) with IFX ($p < 0.001$) [20]. Following, no significant differences were depicted with two regimens of SEC compared with placebo at 6 months as well, 7.7 ± 22.4 vs 11.5 ± 28.2 vs 7.7 ± 22.4 ($p > 0.05$) [24]. We also found no differences at 24 months in the mean rate of uveitis flares between DAC and placebo 1.57 flares/year vs 1.53 flares/year ($p = 0.142$), in the time to the uveitis flare 589 days (95% CI 0–846) vs 732 d (95% CI 0–1.059), $p = 0.620$, or in the uveitis flare severity ($p > 0.05$) [25]. Another study compared pegIFNα2a vs conventional therapy, and showed a mean uveitis flares of 0.8 vs 1.3 ($p = 0.373$) [21]. Finally, we included a RCT in which the mean change in the disease activity index for posterior uveitis at 6 months was, for RTX + MTX group 1.15–0.4 ($p = 0.001$), in the combination of cytotoxic drug group 1.6–0.95 ($p = 0.028$), but there were no differences between groups ($p = 0.77$) [27]. On the other hand, when ocular flares were analyzed by Lightman et al. [26], no significant difference was depicted in the pegIFNα2b group compared with the non-interferon group at year 1 and 3 (31% vs 26%, and 10% vs 12.5%, respectively).

Retinal involvement

Retinal vasculitis was evaluated in two studies [20, 27], retinal thickness in two [22, 23] and macular edema in three [22, 23, 27]. Regarding to retinal vasculitis, the first study reported a tendency to reduce episodes of retinal vasculitis with RTX + MTX (from 2.55 ± 1.46 to 1.75 ± 1.46, $p = 0.057$) not seen in the CFM + AZA group (from 2.3 ± 1.06 to 2.05 ± 1.5, $p = 0.31$), but without differences between groups ($p = 0.24$) [27]. The other study found that a mean number of relapses of retinal vasculitis was reduced during the infusion period with IFX when compared to the pre-IFX period and the conventional therapy group [20]. Two RCTs comparing ADA with placebo assessed mean changes in central retinal thickness at 6 weeks or more. One of them reported significant better results with ADA, difference − 11.4 (95% CI − 20.9 to − 1.8) [22], but not the other one, difference − 2.3 (95% CI − 8.5 to 3.8) [23]. When macular edema was analyzed, the two RCTs exposed above, did not find differences between ADA and placebo in time to macular edema [22, 23]. Another RCT evaluated the mean change at 6 months of an index of retinal, disc and macular edema. In this trial, RTX + MTX group improved it from 1.95 to 1.05 ($p = 0.012$), as well as in the combination of cytotoxic drugs, from 2.3 to 1.5 ($p = 0.014$), and no difference between groups was reported ($p = 0.82$) [27].

Table 2 Main results of the included studies

#	Study	Efficacy	Safety and ocular complications
1	Yamada et al. [19]	Δ VA at 6 m: 97% of eyes in IFX and 93% in CsA improved (≥ 2 lines) or no Δ ($p > 0.05$) Uveitis flares pre vs post-treatment CsA: 3.3 ± 2.4 vs 1.2 ± 1.2 ($p > 0.05$) IFX: 3.1 ± 2.7 vs 0.4 ± 1 ($p > 0.05$) Uveitis flare post-treatment: CsA 1.2 ± 1.2 vs IFX 0.4 ± 1 ($p < 0.05$)	CsA: $n = 1$ neurological symptoms, $n = 1$ renal toxicity IFX: $n = 9$ skin symptoms; $n = 1$ infusion reaction; $n = 1$ leucopenia No serious AE in either group
2	Tabbara et al. [20]	VA at 24 m ($p = 0.005$): ≥ 20/50: $n = 2$ CT vs $n = 5$ IFX 20/50 − 20/200: $n = 18$ CT vs $n = 2$ IFX ≤ 20/200: n = 13 CT vs n = 3 IFX ($p = 0.006$) In the IFX group, vision improvement was faster 2–7 d post-infusion Uveitis flares at 24 m: 6.3 (4–7) CT vs 1.2 (0–4) IFX, $p < 0.001$ At 24 m mean remission time: 5 m CT group vs 17 m IFX group Retinal vasculitis flares ↓ when compared to pre-IFX and to the CT group	CT: $n = 4$ HBP; $n = 5$ ↑creatinine, $n = 3$ ↑ liver enzymes, $n = 2$ leucopenia and thrombocytopenia, n = 5 hyperglycemia, $n = 1$ psychosis IFX: $n = 2$ mild infusion reaction, $n = 1$ perianal abscess Ocular complications at 2 year less frequently with IFX vs CT
3	Jaffe et al. [22]	ADA vs placebo Δ Best VA: − 0.07 (95% CI − 0.11 to − 0.02) Δ VFQ-25: 4.20 (95% CI 1.02–7.38) Δ VFQ-25 distant vision: 1.86 (95% CI − 2.03 to 5.75) Δ VFQ-25 near-vision: 5.12 (95% CI 0.34–9.90) Δ VFQ-25 ocular pain: 10.02 (95% CI 4.86–15.2) Median time to treatment failure 24 vs 13 w Risk of treatment failure at w 6 or later for Any reason: HR 0.5 (95% CI 0.36–0.70) Degree of cells in anterior chamber: HR 0.51 (95% CI 0.30–0.86) VH: HR 0.32 (95% CI 0.18–0.58) Active new inflammatory lesions: HR 0.38 (95% CI 0.21–0.69) Δ Degree anterior chamber cells: − 0.29 (95% CI − 0.51 to − 0.07) Δ VH − 0.27 (95% CI − 0.43 to − 0.11) % Δ Central retinal thickness: − 11.4 (95% CI − 20.9 to − 1.8) Median time to macular edema at w 6 or after: 11.1 vs 6.2 m ($p = 0.23$)	ADA vs placebo Incidence AE 1052.4 per 100 person-yr vs 971.7 per 100 person-yr Incidence of severe AE: 28.8 per 100 person-yr vs 13.6 per 100 person-yr $n = 1$ AE leading to death (ADA)

Table 2 (continued)

#	Study	Efficacy	Safety and ocular complications
4	Nguyen et al. [23]	ADA vs placebo Δ Best corrected VA − 0.04 (− 0.8 to 0.01) Δ VFQ-25: 2.12 (− 0.84 to 5.08) Δ VFQ-25 distant vision: 1.88 (− 2.53 to 6.29) Δ VSQ-25 near-vision: 0.10 (− 4.81 to 4.61) Δ VSQ-25 ocular pain: 0.56 (− 4.56 to 5.68) Time to treatment failure for any reason > 18 m vs 8.3 m Risk of treatment failure for Any reason: HR = 0.57 (95% CI 0.39–0.84) Worsening in best corrected VA: HR 0.33 (95% CI 0.16–0.70) Degree of cells in anterior chamber: HR 0.70 (95% CI 0.42–1.18) VH: HR 0.79 (95% CI 0.34–1.81) Active new inflammatory lesions: HR 0.55 (95% CI 0.26–1.15) Δ Degree anterior chamber cells − 0.14 (95% CI − 0.37 to 0.08) Δ VH − 0.13 (95% CI − 0.28 to 0.11) % Δ Central retinal thickness: − 2.3 (95% CI −8.5 to 3.8) Time to macular edema: HR 0.75 (95% CI 0.34–169)	ADA vs placebo: Incidence AE: 879 per 100 person-yr vs 905 per 100 person-yr Incidence of severe AE: 13.8 per 100 person-yr vs 14.1 per 100 person-yr $n = 2$ AE leading to death, an aortic dissection and cardiac tamponade (ADA)
5	Davatchi_2010 [27]	RTX + MTX group vs CC Δ VA ($p = 0.49$) Δ Disease activity index for posterior uveitis ($p = 0.77$) Δ Retinal vasculitis ($p = 0.24$) Δ Index of retinal, disc and macular edema ($p = 0.82$) Δ TADAI ($p = 0.2$) Δ TIAI ($p = 0.06$)	RTX: $n = 2$ conjunctivitis, $n = 1$ pneumonia; $n = 1$ herpes zoster; $n = 3$ infusion reactions -CC: $n = 1$ conjunctivitis
6	Buggage et al. [25]	DAC vs placebo Δ Best VA ($p > 0.05$) Patients with uveitis flare: 67% vs 50% Nº uveitis flares: 1.57 flares/yr vs 1.53 flares/yr ($p = 0.142$) Time to uveitis flare: 589 d (95% CI 0-846) vs 732 d (95% CI 0–1,059), $p = 0.620$ Uveitis flare severity ($p > 0.05$) Immunosuppressant tapering ($p > 0.05$) Median Δ VFQ-25: +2 vs + 2.5 ($p > 0.05$)	$n = 0$ life-threatening complication or serious opportunistic infection DAC: serious AE 5% Placebo: serious AE 6%
7	Dick et al. [24]	SEC 1 vs SEC 2 vs placebo Δ Best VA ($p > 0.05$) Uveitis flares ($p > 0.05$) % Patients without uveitis flares ($p > 0.05$) % Patients ≥ 3 uveitis flares ($p > 0.05$) Time to first uveitis flare ($p > 0.05$) Mean Δ ISM score: − 1.6 vs − 3.2 vs − 0.5 ($p < 0.05$ SEC 1, 2 vs placebo) Mean Δ VH score (p > 0.05) % Patients with ↓ or no ↑ VH score: 38.5% vs 59% vs 23.1%	SEC 1 vs SEC 2 vs placebo Deaths: 0/1/0 AE [% patients): 82.1%/79.5%/69.2 Serious AE: 15.4%/20.5%/12.8%

Table 2 (continued)

#	Study	Efficacy	Safety and ocular complications
8	Lightman et al. [26]	PegIFNα2b vs non-IFN at yr 1 Patients on ≤10 mg corticosteroid (p > 0.05) Patients on ≤10 mg corticosteroid with ocular disease 54% vs 63% Patients on ≤10 mg corticosteroid with systemic disease 75% vs 61% Ocular patients' rate of ocular flare ($p > 0.05$) Systemic patients rate of ocular flare ($p = 0.192$) Severe ocular flare rate ($p = 0.395$) Severe ocular flares in year 1 ($p = 0.189$) Corticosteroid dose at 1 year 6.5 vs 10 ($p = 0.039$) Mean Δ nº immunosuppressive drugs − 0.29 vs 0 ($p = 0.24$) % Patients on biological agents 1% vs 15.8% ($p = 0.23$) PegIFNα2b vs non-IFN at yr 3 Patients on ≤10 mg corticosteroid ($p = 0.777$) Patients on ≤10 mg corticosteroid with ocular disease 40% vs 56% Patients on ≤10 mg corticosteroid with systemic disease 57% vs 60% Ocular patients rate of flare ($p > 0.05$) Systemic patients' rate of flare ($p = 0.615$) Severe flare rate ($p = 0.704$) Severe flares in year ($p = 0.658$) Corticosteroid dose ($p = 0.309$) Mean Δ nº immunosuppressive drugs ($p = 0.55$) % Patients on biological agents ($p = 0.54$)	$n = 63$ AE ($p < 0.050$) PegIFNα2b significant AE: ocular ischemic event $n = 2$; visual loss $n = 2$; cataract $n = 2$; other ocular $n = 2$; new diabetes $n = 2$; new hypertension $n = 1$; abnormal LFTs $n = 8$; other hematological abnormalities $n = 9$; serious infection $n = 1$; other $n = 2$ Non-IFN significant AE: ocular ischemic event $n = 1$; visual loss $n = 0$; cataract $n = 1$; other ocular $n = 2$; new diabetes $n = 2$; new hypertension $n = 1$; abnormal LFTs $n = 8$; other hematological abnormalities $n = 14$; serious infection $n = 1$; other $n = 1$
9	Hasanreisoglu et al. [21]	PegIFNα2a vs CT VA in IFNα2a improved 18.7%, remained stable 65.6%, decreased 15.7% Mean uveitis flares 0.8 vs 1.3 ($p = 0.373$)	IFNα2a: $n = 1$ leucopenia, all patients had fever and flu-like symptoms CT: $n = 1$ anemia, $n = 1$ liver abnormalities

AE adverse events, *ADA* adalimumab, *CC* combination of cytotoxics (CFM + AZA + MTX), CI = confidence interval; *CsA* cyclosporine A, *AZA* azathioprine, *CT* conventional treatment, *CFM* cyclophosphamide, *DAC* daclizumab, *TADAI* total index adjusted to the activity of the disease, *TIAI* total index of inflammatory activity, *HBP* high blood pressure, *IFX* infliximab, *IFNα2a* interferon α2a, *m* months, *MFN* mycophenolate mofetil, *HR* hazard ratio, *pegIFNα2b* peginterferon α2b, *pegIFNα2a* peginterferonα2a, *RTX* rituximab, *SEC* secukinumab, *VFQ-25* visual function questionnaire, *VA* visual acuity, *VH* vitreous haze, *w* week, *yr* year, *ISM* concomitant medication use composite score, *LFT* liver function tests

Indexes of ophthalmological inflammatory activity and vitritis

We included one RCT that analyzed the inflammatory activity using the total index adjusted to the activity of the disease (TADAI) and the total index of inflammatory activity (TIAI) [27]. At 6 months, the mean change in the TADAI in the RTX + MTX group was from 41.7 to 34.7 ($p = 0.009$); in the CC from 43.4 to 39.8 ($p = 0.052$); but there were not differences between groups ($p = 0.2$). The same way the mean change in the TIAI at 6 months, was, in the RTX + MTX group from 20.4 to 12.1 ($p = 0.001$); in the CC from 20.2 to 16.4 ($p = 0.021$); without significant differences ($p = 0.06$) [27].

On the other hand, three RCTs included vitreous haze (VH) from 0 to 4 + as outcomes [22–24]. The first one compared two SEC regimens and placebo. The authors found the same mean change in the VH score in all study groups: − 0.5 vs − 0.5 vs − 0.5 ($p > 0.05$ between groups), and a rate of patients with a decrease or no increase in the VH score of 38.5% vs 59% vs 23.1% (placebo) [24]. The other two RCTs compared ADA with placebo, the one with patients with active uveitis showed that ADA improved significantly more than placebo the VH score [22], but the other one (inactive uveitis) did not report differences between groups [23].

Visual functioning

In two RCTs, the visual functioning was analyzed using the NEI-Visual Functioning Questionnaire-25 (VFQ-25) score [22, 23]. One of them (active uveitis patients) reported a significant improvement in the ADA group compared with placebo in the mean change of the VFQ-25 score as well as in the near vision and ocular pain subscores, but not in the distance vision subscore ($p = 0.35$) [22]. The other RCT that also compared

ADA with placebo in patients with inactive uveitis no differences were found between groups [23].

Ophthalmological complications

Tabbara and colleagues found that ocular complications at 2 years were seen less frequently in the IFX group than in the conventional therapy group. No IFX patient developed phthisis bulbi or retinal detachment. However, in the other group 9% of patients had phthisis bulbi, 9% enucleation, and 6% developed retinal detachment. Optic atrophy was observed in 60% of patients in the conventional therapy group and in 30% in the IFX group [20].

Corticosteroid-sparing effects and other saving effects

These effects were analyzed in four RCTs [22, 24–26]. One demonstrated that without glucocorticoid support, ADA controlled multiple aspects of uveitic inflammation and was associated with a lower risk of uveitis flare and a longer time to a uveitis flare than placebo [22]. Another RCT developed a score consisting of a composite score of the sum of all immunosuppressant's doses. This trial compared two SEC regimens and placebo, and reported that at 6 months of treatment, the mean reduction in the score was significantly greater in the SEC groups compared with placebo [24]. A score based on the total number of immunosuppressant drugs and their doses, including prednisone or equivalent, was also used in another RCT [25]. In this case, no significant differences were registered between DAC and placebo at 24 months ($p=0.47$) [25]. Finally, Lightman et al. found a lower corticosteroid dose at 1 year patients on IFNα2b compared with those on other treatments, 6.5 vs 10 ($p=0.039$), but at 3 years this difference was not statistically significant, 8.8 vs 8.8 ($p=0.309$). On the other hand, the author reported no differences at 1 and 3 years in the mean change in the number of immunosuppressive drugs [26].

Safety

The rate of AE was recorded in all studies [19–27], being infusion reactions and skin lesions more frequent among patients treated with biological therapies, and hypertension, renal and hepatic abnormalities, and cytopenias among those treated with synthetic immunosuppressants (see Table 2 for more details).

Discussion

We conducted a systematic literature review to compare the efficacy and safety of biologic therapy with CsA, AZA or placebo in Behçet's disease associated uveitis.

When we analyzed the efficacy, in general, we did not find clear differences in many disease outcomes between the study drugs or placebo. Only IFX and ADA in active patents showed some superiority when compared with traditional immunosuppressants or placebo. On the other hand, safety outcomes were those as expected taking into account the type of drugs that were evaluated.

Regarding to VA, both biological therapies and traditional immunosuppressants improved it, but in most of the studies there were not statistical differences among them. Moreover, when compared with placebo, the results were quite the same [19–25, 27]. Uveitis flares were collected in most of studies, but only IFX showed significant better results compared with classical immunosuppressant drugs [19, 20]. On the other hand, in patients with retinal involvement, and compared with a combination of cytotoxic drugs, RTX plus MTX could not demonstrate a significant higher effect when retinal vasculitis was present and in an index of retinal, disc and macular edema, at least in the short term [27]. However, this finding might be due to the time needed to detect a clinical improvement when using RTX. In the long-term, IFX showed a lower number of flares (after 3 months in remission) than the combinations of CsA plus AZA or MTX, but in this case authors did not report if this difference was statistically significant [20]. We also included two RCTs that compared ADA with placebo [22, 23]. They found that ADA was superior to placebo in the percentage of change in the central retinal thickness, although it was only significant in the study in which patients presented active uveitis [22], not in the RCT that included patients with inactive uveitis [23]. We consider that in patients with inactive uveitis is more difficult to detect differences and might reflect a protective effect. However, there were not differences in these RCTs in terms of time to macular edema. Following, we assessed different ophthalmological inflammatory activity outcomes, and the results were very similar, biologic therapy did not demonstrate a clear superiority when compared with traditional immunosuppressant drugs, although both groups showed improvements [22, 23, 27]. Regarding to corticosteroid-sparing effect of drugs, we also found that, at least in the short term, ADA compared with placebo and IFNα2b with other drugs were significantly superior. When the effect on doses and number of immunosuppressant drugs, SEC showed superiority compared with placebo at 6 months, but not DAC and IFNα2b. Finally, safety outcomes were the expected with the use of these drugs [19–27].

Safety outcomes did not show new safety signal. As expected, infusion reactions and skin lesions more frequent with biological therapies, and hypertension, renal and hepatic abnormalities, in patients with synthetic immunosuppressants.

In the literature, there is little evidence on the use of biologicals in ocular disease of Behçet's patients. The

majority of publications are case series, without a comparator. Of the existing publications, most analyze patients on anti-TNF therapy, mainly IFX and ADA. The publications of Cordero-Coma et al. [28] that included an important number of patients with Behçet, described an improvement in the ocular inflammation with anti-TNF (ADA and IFX). However, all of this evidence comes from observational studies in daily clinical practice. In relation to IFN2a, Sobaci and colleagues [29] evaluated patients refractory to corticosteroids and conventional immunosuppressants, and a significant improvement in acute flares of uveitis and VA was observed after 1 year of treatment. Park et al. [30] described five patients treated with IFNα2a, reducing the rate of uveitis flares and the use of corticosteroids, but without significant improvement in VA.

This systematic literature review presents some limitations. The main one is the low level of evidence in general, except for some RCTs. The inclusion criteria for Behçet's disease were not homogeneous in all studies and the follow-up was in general short. Although most of the selected studies only included patients with Behçet's disease, two of them included a mixed population [22, 23]. We found a great heterogeneity regarding to the outcome measures that limit the interpretation of the results. On the other hand, some studies with a high level of evidence such as the RCTs of ADA present a rather small sample size limiting their representativeness. In fact, the efficacy of ADA in was not sub-analyzed in patients with Behçet. Besides, drugs such as DAC and SEC are usually not used in routine clinical practice. Taking into account all of this, it was not possible to perform a meta-analysis in this systematic literature review.

In summary, we observed that, in patients with ocular involvement both classical immunosuppressant drugs and biologic therapies can improve visual outcomes. When compared both groups of treatment, depending on the outcome, there was not a clear superiority of biologics, although there might be a trend to biologic superiority in reducing the rate of uveitis flares in the short and medium terms or as corticoid sparing drugs.

Due to the limited evidence and quality found in the available results, well-designed comparative studies to assess the effect of a novel drug in the uveitis of Behcet's are needed so that a robust conclusion can be drawn. For that purpose we would also need to use uniform outcome measures and patient-reported outcomes such as quality of life.

Author contributions AU-A, RB and EL participated in the study design. MSG, KV-O, LFP and AU-A participates in the study selection and data collection. All of the authors took part in the rest of the study phases, contributed in this article discussion and reviewed the final version.

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Compliance with ethical standards

Conflict of interest RB has received grants/research supports from Abbvie, MSD, and Roche; Consultation fees/participation in company sponsored speaker´s bureau from AbbVie, Pfizer, Roche, Bristol-Myers, Janssen, Lilly and MSD. EL has received grants/research supports from Abbvie, MSD, Roche, Pfizer, Bristol-Myers, MSD, Novartis, Astellas, Sanofi.

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