Seminars in Arthritis and Rheumatism 000 (2021) 151944

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Efficacy and safety of the optimisation of biological therapy in non-infectious uveitis: Systematic review

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ARTICLE INFO

Keywords:
No-infectious uveítis
Biological therapy
Optimisation
Treatment

ABSTRACT

Objective: To conduct a systematic critical review of the literature on the efficacy and safety of biological therapy (BT) optimisation in non-infectious uveitis (NIU).
Methods: Searches were conducted (PubMed, Embase, Cochrane and conference abstracts) up to March 2021. The study population comprised patients with NIU in remission after BT. We analysed BT optimisation strategies. The main outcome measures were efficacy and safety. To assess the risk of bias, the ROBINS-1 tool was used. A qualitative review of the data was performed to assess heterogeneity and bias. Evidence tables (study characteristics and outcomes) were generated, and quantitative synthesis was performed if data were homogeneous.
Results: We selected 11 studies (prospective and retrospective) including 513 patients. The studies were at moderate/high risk of bias and there was considerable variability between studies in sample size, underlying diseases, definitions and outcome variables. Criteria for starting optimisation were not uniform. All BTs optimised were TNF inhibitors. Optimisation could be attempted after 3–6 months in remission. Relapse occurred in 25–50% of patients but was controlled after dose re-escalation or BT switching. No safety issues were identified.
Conclusions: The optimization of BT (with TNF inhibitors) has been applied in patients with NIU in remission. There is no consensus on criteria for attempting BT optimisation and protocols are heterogeneous. There is a least moderate risk of bias, so no robust conclusions on efficacy and safety of optimization can be reached. Preliminary evidence suggests that relapses might be controlled using standard doses. Larger studies using uniform criteria are needed.

Introduction

Non-infectious uveitis (NIU) is a heterogeneous group of diseases associated with inflammation of the uvea [1,2] that is potentially severe (accounting for 10–15% of cases of total blindness [3,4]) and can be the expression of a systemic or idiopathic autoimmune disease. NIU may require long periods of treatment to avoid long-term damage and irreversible vision loss [2,5-7]. They may respond to glucocorticoids, other immunomodulatory drugs and/or biologics, administered sequentially or in combination. Biological therapy (BT) has shown to be effective, and in other autoimmune disorders, can be optimised [5]. In patients with NIU, however, it is not known whether such optimisation is effective and safe in the long term. Our objective was to conduct a systematic review of all data published in the literature on BT optimisation in NIU.

Methods

A protocol for a systematic review of the literature was designed using the PICO framework and registered with PROSPERO (registration number 236,852), following the recommendations of the Cochrane Collaboration and the PRISMA checklist. The study population (P) comprised patients with NIU (regardless of patient age, the severity and anatomical location of the inflammation, and the disease underlying the uveitis) on BT (I) in whom optimisation was undertaken (regardless of the type of BT, dose, treatment duration, route of administration, previous treatments, and the point at which optimisation was attempted, the optimisation strategy used, etc.). No restrictions were placed on the comparator (C), and even papers with no comparison group were included. The main outcome measures (O) assessed were the efficacy and safety of optimisation. We limited our search to studies on humans, reported in English or Spanish, excluding basic research and studies on animals.

We developed strategies for searches of each of the databases (Supplementary table S1 to S3) from their creation to March 2021,

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https://doi.org/10.1016/j.semarthrit.2021.11.010
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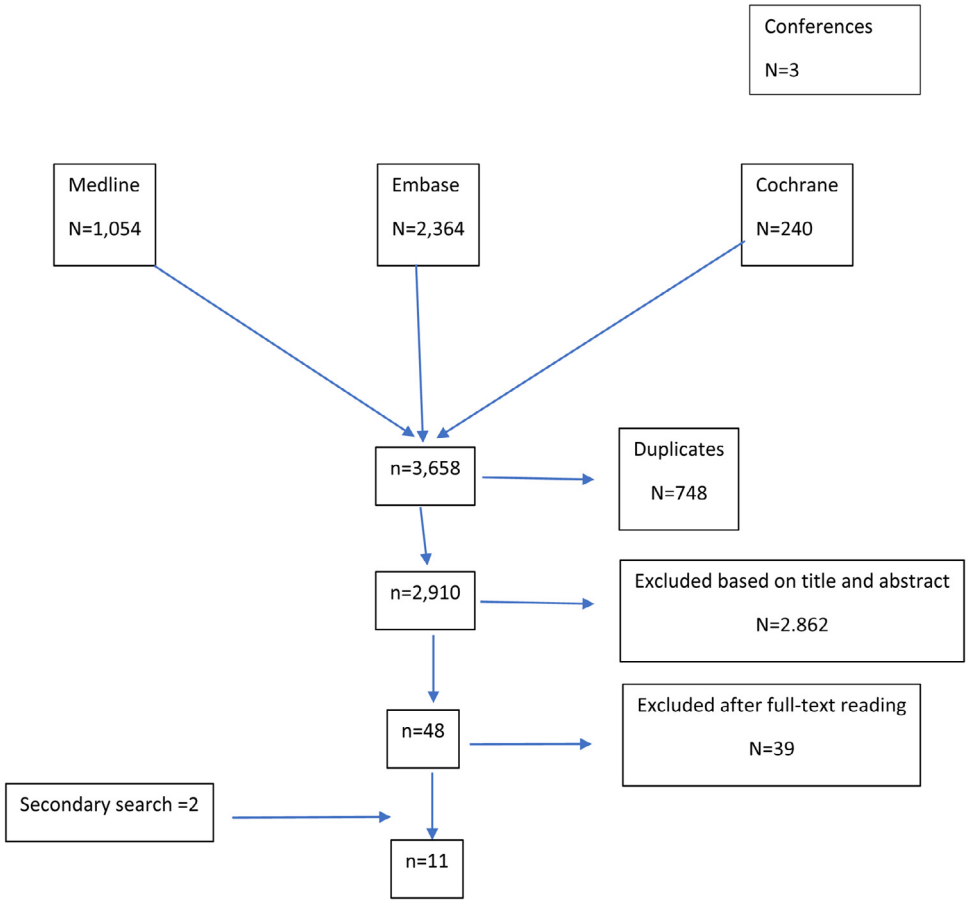

Fig. 1. Flow of the studies through the selection process.

and literature from international conferences (Supplementary table S4). The publications retrieved were entered into a reference management database (EndNote®). Two reviewers conducted a first screening by title and abstract, selecting papers for which 1) selection criteria were met, 2) it was unclear whether criteria were met, or 3) no abstract was available. Subsequently, these papers were downloaded and reviewed in detail (full reading), for the final selection of the papers included. Data were collected independently by two reviewers in pre-designed and tested forms. The tools used to assess the risk of bias of these non-randomized observational studies was ROBINS-I [8]. The scoring criteria used to classify the methodological quality of the studies are those indicated by the ROBINS-1 tool itself.

The data collected included variables related to 1) the study population such as sample size, sociodemographic characteristics, NIU (type of uveitis, duration), etc., 2) the BT and its optimisation, such as the therapy type, administration route and duration, previous treatments, and strategy for therapy optimisation used; 3) outcomes of interest; and 4) the quality of the studies.

The data were reviewed qualitatively, based on an evidence table in terms of numbers and types of studies, study quality, population included, BT and optimisation strategy used, and outcomes analysed. Further, outcomes were analysed in detail, seeking to identify potential heterogeneities and biases. Another evidence table was created to present the data on optimisation and the outcomes of interest (efficacy and safety). Quantitative synthesis (meta-analysis) was only to be performed if data were homogeneous.

Results

The systematic review retrieved a total of 3658 publications. After removing duplicate studies, screening by title and abstract, and full-text reading (extending this process to references in papers included), only 11 papers were considered to meet the selection criteria (Fig. 1). List of excluded publications and the reasons for their exclusion (Supplementary table S5). Tables 1 and 2 describe the 11 studies finally included [9–19], these involving a total of 513 patients. Though some were prospective [13,16,17,19], most of the studies were observational and retrospective [9-12,14,15,18]. The follow-up ranged from a minimum of 12 months to several years. Given the existing evidence, we wanted to show all the articles found, despite the fact that some did not present a control group. We assume that the inclusion of descriptive observational studies (case series) without a control group implies a low level of evidence and may compromise the performance of a meta-analysis.

In the total population, there was a predominance of men, the mean age was 36 years old, and the most common underlying condition was Behçet's disease. As well as patients with Behçet uveitis (n = 8 studies) [9,10,12,14-16,18,19], the studies described uveitis associated with juvenile idiopathic arthritis (JIA) (n = 2) [11,18], ankylosing spondylitis (AS) (n = 2) [13,17] or idiopathic uveitis (n = 1) [18]. The patients had uveitis (posterior, intermediate or panuveitis) refractory to glucocorticoids, and had achieved remission with a BT after the failure of at least one disease-modifying antirheumatic drug (DMARD).

The criteria for attempting optimisation were not uniform, the minimum duration of sustained remission with the BT required ranging from 3 to 12 months. Patients were allowed to be on DMARDs and/or glucocorticoids and even to have previously been treated with tumour necrosis factor (TNF) inhibitors. The intervention involved infliximab (IFX) in seven studies, adalimumab (ADA) in two studies and etanercept (ETN) in another two. No studies reported the optimisation of BTs other than TNF inhibitors, and hence, no other biologics

Table 1
Evidence table: main characteristics of the studies included.

Study	Population	Intervention/s	Control	Outcome measures	Overall risk of bias
Adán, 2010 [9], observational retrospective study, follow-up to 20 months	-*n* = 4 patients, Behçet disease with recurrent posterior uveitis, refractory to at least one DMARD. 75% women; mean age 33 years. Pred 5–10 mg daily, 3 on ciclosporin, 3 on AZA	-IFX 5 mg/kg iv at weeks 0, 2 and 4 weeks (induction) and then every 8 weeks -DMARD -Systemic corticoids	No	-Uveitis flares (↑ ≥50% inflammation and retinal vasculitis score) -Flare-free survival -Macular oedema by OCT -VA -Vitreous cell grade (0–4) -Retinal vasculitis (0–4) -Drug-free remission	Serious risk
Al Rashidi, 2013 [10], observational, retrospective study, mean follow-up of 44 months (range 12- 112)	-*n* = 19 patients (*n* = 38 eyes), Behçet disease with severe uveitis refractory to DMARDs. 94.7% male, mean age 25 years, *n* = 4 on MP 1 g/d every 3 *d* + pred 1 mg/kg/d, *n* = 15 on pred 1 mg/kg/d, 16 on ciclosporin, 2 on AZA, 1 on MMF	-IFX 5 mg/kg iv at weeks 0, 2 and 4 weeks (induction) and then every 8 weeks (except in 4 patients, every 6 weeks) -DMARD -Systemic GCs	No	-Uveitis flares -Flare-free survival -VA -Control of inflammation, CME -DMARD dose ↓ or discontinuation of -AEs	Serious risk
Breitbach, 2017 [11], observational, longitudinal and retrospective study, follow-up between 2006 and 2013	-Cohort of patients with JIA and uveitis refractory to topical treatment, pred ≥1 mg/kg/d and ≥ 1 DMARD, 68 patients (18%) treated with ADA, but study only included the 59 patients with good response within the first 6 months (primary response) on ADA. 79% women, 88% anti-nuclear antibody positive monoarthritis vs 12% polyarthritis. Mean duration of uveitis 6.3 years, 72% had ocular complications. 76% on MTX, 18% on AZA, 15% on ciclosporin, 12% previous TNF inhibitor: ETN, or IFX	-ADA 24 mg/m^2 body surface area (max 40 mg/15 d). ADA discontinued in *N* = 20 patients	Yes, *N* = 39 patients (66.1%) remained on ADA	-Anterior chamber cell grade - Improvement in best corrected VA -Secondary failure: poor response to ADA in the following 6 months -Remission of uveitis -Recurrence or complications (synechiae, vitritis, CME) -Discontinuation of GC, AEs -Disappearance of CME and no worsening -Worsening of arthritis	Moderate risk
De Simone, 2020 [12], Retrospective study from 2003 to 2919	-*n* = 22 patients (39 eyes). Consecutive patients with Behçet disease and refractory uveitis (posterior, intermediate and panuveitis) treated with IFN Alpha-2a or IFX ≥ 3 months. -Inclusion criteria: Failure to respond to ≥ 1 DMARD or reactivation on reducing pred < 7.5 mg daily. Complete follow-up ≥ 12 months after starting BT. - Exclusion criteria: previous BT 14 male patients, mean age 29 years. Refractory to GC (96% of patients) and DMARDs (82% of patients), with no differences between groups. Mean time from diagnosis to BT: 24 months	- GCs and DMARDs discontinued before starting BT. -*n* = 15 patients (29 eyes) with predominantly exudative/oedematous condition with CME, given IFN alpha-2a sc at a dose of 3 million IU/3 times a week. If no response, dose increased by 3 million IU/d for 1 month. After response, dosage ↓ to 3 million IU twice weekly and then discontinued. Treatment algorithm customised. If reactivation, IFN administered again at a dosage depending on activity. -*n* = 7 patients (10 eyes), with an ischaemic/neovascular phenotype and/or macular ischaemia, given IFX 5 m/kg at weeks 0, 2 and 6 and then every 6–8 weeks.	No	-Main outcome measure: complete remission after 3 months (anterior and vitreous chamber cell grade 0, no vasculitis/papillitis or CME) - Secondary outcome measure: flare during treatment or after treatment withdrawal. Changes in best corrected VA and macular thickening. Side effects or AEs	Serious risk

(*continued on next page*)

Table 1 (*Continued*)

Study	Population	Intervention/s	Control	Outcome measures	Overall risk of bias
De Stefano, 2014 [13], Prospective study from 2007 to 2010, follow-up of patients after 1 year	-*n* = 38 patients with AS Inclusion criteria: Active disease ≥ 1 year, BASDAI >4 with NSAIDs, age range 18–65 years. 76% men. Mean age 44 years. 87% HLA B27+. Mean disease duration of 3.4 years. 15% of patients had arthritis, 10% enthesitis, 8% uveítis (3 patients). Exclusion criteria: significant comorbidities.	Regimen: ETN 25 mg twice weekly. Response assessed after 12 and 16 weeks. If clinical remission, ETN ↓to 25 mg weekly. If clinical remission, at 24 and 28 weeks, ENT ↓ 25 mg fortnightly. If partial remission at weeks 12 and 16, ETN maintained at 25 mg twice weekly.	No	- Primary endpoint:% of patients achieving ASAS20, ASAS40, and ASAS 5/6 responses and partial remission after 12 weeks - Secondary endpoints:% patients with partial remission after 48 weeks with ETN 25 mg weekly and% with another treatment regimen -AEs	Serious risk
Kawaguchi, 2014 [14], retrospective study from 2000 to 2012, follow-up ≥ 12 months, before and after the BT	-*n* = 43 Behçet uveitis, refractory to GCs and DMARDs, consecutively treated with IFX, but BT only discontinued in 7 patients. 36 male patients, mean age 39 years	-IFX 5 mg/kg at weeks 0, 2 and 6 weeks and then every 8 weeks	No	- Recurrence rate of uveitis - Best corrected VA - Slit lamp biomicroscopy - Indirect ophthalmoscopy	Serious risk
Köse, 2020 [15], Retrospective study from 2010 to 2018	-*n* = 8 patients with Behçet uveitis in whom IFX was discontinued after sustained remission and ≥12 months of treatment. Five women (62%). Mean age 41 years. 12 years with Behçet disease, but mean of 10 years with uveitis (88% bilateral). All on AZA, 62.5% on ciclosporin and 62.5% on IFN	-IFX 5 mg/kg at weeks 0, 2 and 6 and then every 4 weeks After 6 months of inactivity, ↓ to every 6 weeks. After a further 6 months, ↓ to every 8 weeks. After 12 months of remission, withdrawn completely -AZA 2 mg/kg/day	No	- Clinical remission: complete remission of inflammation and vasculitis without flares for ≥ 12 months -Recurrence: ≥ 50% ↑ in inflammation and retinal vasculitis - Number of flares before, during and after IFX withdrawal - Best corrected VA, OCT - Slit lamp biomicroscopy, tonometry, angiography - Indirect ophthalmology	Serious risk
Martín-Varillas, 2021 [16], Prospective, open-label, multicentre study (35 Spanish uveitis units). 4-year follow-up	-*n* = 103 white patients (185 eyes). Behçet uveitis refractory to GC and ≥ 1 DMARD, treated with IFX as first-line BT ≥ 24 months, and clinical remission > 3 months. No baseline differences between groups. 55 male patients, mean age 40 years. Bilateral uveitis (80%). Immunosuppression score 9.1 ± 4.1	- Three pulses of MP at doses of 500–1000 mg daily in cases of severe uveitis –3–5 mg/kg iv bolus of IFX at weeks 0, 2 and 6 weeks, then every 4–8 weeks until clinical remission > 3 months. Shared decision-making with the patient and treatment optimised (extending the dosing interval and/or reducing the dose)	Yes, patients with refractory Behçet uveitis, treated with IFX ≥24 months and clinical remission but dose and dosing interval unchanged	- Efficacy and long-term safety of IFX - Assessment of whether optimisation after remission is efficacious, effective and cost-effective -Macular thickness, intraocular inflammation, fluorescein angiography, Nussenblatt vitreous haze scale -GC-sparing effects -Degree of immunosuppression assessed using the semi-quantitative scale proposed by Nussenblatt	Moderate risk
Park, 2016 [17], observational, prospective, clinical practice study from 2004 to 2013	-*n* = 134 patients with AS in remission after ETN ≥ 1 year, follow-up ≥ 6 months after dose reduction. 16% women. Mean age 47 years. Mean duration of AS of 6.5 years. Low doses of GCs, NSAIDs, SSZ and MTX allowed. In 90% of the patients, it was the first TNF inhibitor	ETN 50 mg weekly until remission ≥ 1 year, follow-up ≥ 6 months after dose ↓. No consistent regimen for optimisation but initially 50 mg weekly, considering dose ↓ or interval ↑ in patients who achieved clinical remission, and then 25 mg weekly if patients remained in remission ≥ 6–12 months. Temporary interruption of treatment or dose ↑ allowed. Interruption >3 months considered withdrawal	Yes, after remission of ≥ 1 year, dose maintained	- Efficacy and safety of the optimisation with ETN -AEs, including uveitis - Drug survival - Clinical factors with an impact on drug survival in both groups (for subsequent univariate and multivariate analysis)	Moderate risk

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Table 1 (*Continued*)

Study	Population	Intervention/s	Control	Outcome measures	Overall risk of bias
Shakoor, 2014 [18], retrospective study from 1998 to 2010	*N* = 18 patients, uveitis in remission without GC after IFX, IFX is reduced/withdrawn and assessment of time to recurrence. 67% of women; uveitis was anterior, posterior and panuveitis in 39%, 17% and 39% of cases, respectively; 22% of patients had Behçet's disease, 22% JIA and 44% idiopathic uveitis. 9 patients on MTX and 6 on MMF.	-IFX 5−10 mg/kg/d, every 4−8 weeks -After remission with GC, IFX withdrawn	No	-Groups with and without flares compared in terms of: comorbidity, flare-free survival, uveitis characteristics, best corrected VA, anterior chamber cell grade, uveitis, vitritis. -GC-sparing effect	Serious risk
Martín-Varillas, 2018 [19], multicentre, prospective, open-label study (35 Spanish uveitis units). 4-year follow-up	-*n* = 65 Behçet uveitis, refractory to GCs and ≥ 1 DMARD, treated with ADA ≥ 12 months and in remission ≥ 3−6 m. 39 men, mean age 39 years. 69% HLA B51+. Duration of uveitis before study: 48 months (range 12−60). No differences in the use of DMARDs. Mean dose of pred at ADA initiation slightly lower in the optimised group (23.4 mg daily vs 28.7, $p = 0.35$)	-*n* = 23 patients (42 eyes); 14 (61%) HLA 51+ ($p = 0.26$). -ADA 40 mg fortnightly. After remission with ADA, joint decision between doctor/patient and optimisation performed by extending the dosage interval: initially every 3 weeks and then every 4, 6 and 8 weeks until withdrawal	Yes -*N* = 42 patients (72 eyes), 29 HLA 51+ (74%). with Behçet uveitis on ADA in remission but ADA 40 mg/15 d maintained	-Main outcome measures: efficacy, safety and cost-effectiveness in optimised and non-optimised groups -Assessment of ocular inflammation (anterior chamber cell grade, vitritis, retinal vasculitis), macular thickness on OCT, best corrected VA, fluorescein angiography, GC-sparing effect -Assessment of vitritis using the Nussenblatt scale	Moderate risk

Abbreviations: ADA: adalimumab; AE: adverse event; AS: ankylosing spondylitis; AZA: azathioprine; BT: biological therapy; CME: cystoid macular oedema; d: day; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GC: glucocorticoid; IFN: interferon; IFX: infliximab; JIA: juvenile idiopathic arthritis; MMF: mycophenolate mofetil; MP: methylprednisolone; OCT: optical coherence tomography; pred: prednisolone; VA: visual.

were included in this systematic review. Many of the studies did not have a comparison group, exceptions being those of Martín-Varillas et al. [16,19], Park et al. [17] and Breitbach et al. [11].

Regarding outcome variables, the data collected were not homogeneous either. In general, researchers collected data on variables related to 1) physical examination, 2) flares in disease activity, 3) safety; and 4) other relevant clinical data (on disease activity) and data on cost-effectiveness.

We consider that a therapy is being optimised when it is possible to gradually reduce the standard dosage while maintaining the initial benefits. This process can be repeated, provided that remission is maintained. In some cases, it may be possible to stop treatment completely, but this is not the objective *per se*, rather the goal is to maintain the clinical benefit and reduce the incidence and severity of adverse events (AEs). Notably, in four of the studies included, there was no optimisation in the narrow sense we describe (de-escalation) [9−12]. In these studies, after reaching remission, the treatment was completely withdrawn and patients' course was observed. Taking this approach does not imply reactivation of the disease in all cases, but it is more likely.

Specifically, Adán et al. [9], after sustained remission for over 6 months with IFX, withdrew the BT. Two of their four patients remained in remission in the long term, with a mean follow-up of 7.5 months, and their visual acuity (VA) remained stable. In the other two patients, reactivation was treated with ADA (40 mg/15 days). By the end of the study, all of the patients were again in remission.

In the study by Al Rashidi [10], the BT was discontinued after complete remission of at least 22 months. Nearly half (*n*=9, 47%) of their patients achieved remission, but only a quarter (26%) remained in remission for at least 19 months. Complete remission was maintained for a mean follow-up period of 24.66 ± 5.5 months. It was possible to withdraw glucocorticoids in 74% of the patients and DMARDs in 40%. Notably, 94.7% of patients did not experience AEs, but one had a severe infusion reaction. Ten patients (53%) developed antinuclear antibodies and anti-DNA antibodies, with no associated clinical signs or symptoms of lupus. Eight patients (42%) underwent intraocular surgery and no exacerbation of the uveitis was observed. Overall, the authors observed reactivation of the uveitis in 44% 0of their patients after around 3 to 10 months.

Breitbach et al. [11] described a cohort of 59 patients with JIA who had uveitis refractory to prednisone >1 mg/kg and at least 1 DMARD or even which failed to respond to another TNF inhibitor, were treated with ADA at a dose adjusted for body surface area and achieved primary remission after at least 6 months of treatment. The authors considered two groups: patients who remained on ADA to the end of the study and those who discontinued ADA for any reason (*n*=20). ADA was discontinued due to AEs in 4 cases, long-term remission (≥2 years) in 2, and secondary treatment failure in 12, and for another reason in 1. amongst those with long-term remission, uveitis reactivation was observed in one case (6 months after discontinuation). amongst those with secondary treatment failure, uveitis and arthritis reactivation were observed in eight and four cases respectively. A total of 14 patients were switched to another BT.

De Simone et al. [12] treated all cases of refractory Behçet uveitis with interferon (IFN) alpha-2a if the condition was predominantly exudative/oedematous, following an established tapering strategy, and with IFX if the phenotype was ischaemic/neovascular, with the standard regimen initially and then every 6−8 weeks. Glucocorticoids and DMARDs were discontinued. After the BT was withdrawn, the rate of relapse was low in both groups, five patients experiencing flares (25%), one and four in the groups on IFN and IFX, respectively. The mean flare-free survival was 153 months with IFN and 91 with IFX.

De Stefano et al. [13] conducted a prospective study of patients with ankylosing spondylitis treated with etanercept (ETN). These authors describe a well-defined protocol for BT optimisation based

Table 2
Evidence table: optimisation and outcomes.

Study	Optimisation or other procedure	Efficacy	Safety
Adán, 2010 [9]	- after ≥ 6 months in remission, systemic GC, DMARD and IFX withdrawn - MNI 12.7 (range 11–14) - If flare, ADA 40 mg sc/15 d	-flares in *n* = 2 patients, 50% (*n* = 2 eyes) -flare-free survival: 4 years 6 months -VA stable in 7 eyes at 6 months after IFX withdrawal -complete remission at most recent appointment in *n* = 4	-*n* = 2 patients continue in remission after a mean of 7.5 months (range 6–10) -*n* = 4 complete remission at most recent appointment
Al Rashidi, 2013 [10]	- After complete long-term, remission IFX withdrawn - Interval between starting of IFN and its withdrawal 22–87 months (mean 56) MNI 30.4 (range 13–43)	- remission achieved in *n* = 9 patients, but only 5 (26%) remain in complete remission for mean follow-up of 24 months (range 19–31) - uveitis flare in *n* = 4 (44%) - flare-free survival 3–10 m -pred and DMARDs withdrawn in 74% and 40% of patients, respectively	-no AEs in 94.7% - severe infusion reaction in 1 patient –10 patients (53%) ANA+/DNA+ without lupus signs or symptoms - 42% of the patients underwent intraocular surgery without signs of exacerbation: 15 eyes for cataracts, 3 eyes for glaucoma -no exacerbation observed in 8 surgical procedures after BT
Breitbach, 2017 [11]	After 6 months on ADA with a primary response, treatment withdrawn in 20 patients but ADA maintained in 39 patients (66.1%)	ADA treatment discontinued in 20 patients after mean of 31 months, for the following reasons: -Long-term remission, ≥2 years (1.47 per 100 patient years), *n* = 2. -Secondary treatment failure, *n* = 12 (60%) -AEs (50% switched to another BT, 50% to a DMARD), *n* = 4 -Other (no further coverage by insurance company), *n* = 1 After withdrawal: –6 patients continued with previous DMARD –14 patients switched to another BT: 6 continued with IFX, 3 to tocilizumab, 2 abatacept, 1 golimumab, 1 ETN and 1 rituximab	-One patient from who ADA was withdrawn due to long-term remission showed reactivation after 6 months -After secondary treatment failure, reactivation of uveitis in 8 and arthritis in 4 patients
De Simone, 2020 [12]	IFN alpha-2a 3 million IU/3 times a week, sc. If no response, increase to 3 million IU/d for 1 m. After response, reduce to 3 million IU twice weekly and withdraw. Customised therapeutic algorithm. If reactivation, IFN restarted depending on activity IFX 5 mg/kg at baseline at after 2 and 6 weeks, and then every 6–8 weeks, depending on response	-Complete remission during treatment: 12 patients (80%) with IFN and 5 (71%) with IFX -Treatment withdrawal possible in 70% on IFN and 57% on IFX - Loss of efficacy: 1 patient on IFN after 5 months -Mean time to discontinue treatment: 18 months (95% CI: 8.6–27.3), this being longer in patients on IFN: 44 months (95% CI: 14.6–73.4) vs 12.6 months (95% CI: 11–14,3) in patients on IFX. 2 patients on IFN still on this therapy at the end of follow-up. - Complete remission after treatment withdrawal achieved in 16 patients (80%), 12 (92%) on IFN and 4 (57%) on IFX.	-Flares after treatment withdrawal: 5 patients (25%). 1 in IFN arm, 4 in IFX arm -Flare-free survival: 153 months on IFN and 91 months on IFX -Good tolerance and no serious AEs in either group -The majority of patients achieved remission without uveitis, with good long-term outcomes -Uveitis recurrence rate relatively low in both groups: 23% during treatment and 22% after BT withdrawal
De Stefano, 2014 [13]	Optimisation protocol: initial regimen of ETN 25 mg twice weekly. Response assessed at 12 and 16 weeks. If partial remission, ETN reduced to 25 mg weekly. If partial remission at 24 and 28 weeks, ETN reduced to 25 mg fortnightly. Final assessment at 48 weeks.	At week 12: patients (%) -Partial remission: 21 (55%) -No response: 8 (21%) At week 24: - Partial remission: 20 patients (52.5%) - Reactivation (uveitis): 1 patient returned to 2 doses/week At week 36: - Partial remission: 16 (42%) on fortnightly doses - Reactivation: 4 patients (10.5%) returned to 1 dose/week At week 48: - Partial remission: 14 patients (37%) - AEs: 2 patients At the end of follow-up: -Remission: 18 patients (47%) -One dose a week: 4 patients (10%) -Fortnightly doses: 14 patients (37%)	- No statistically significant differences in AEs with different doses -Uveitis remained active despite increase in dose

(*continued*)

Table 2 (*Continued*)

Study	Optimisation or other procedure	Efficacy	Safety
Kawaguchi, 2014 [14]	- Withdrawal of IFX for various reasons and assessment of the uveitis flare frequency. Previous DMARD treatment restarted	-AEs: 10 patients (23%) - Complete follow-up: 7 patients, with complete remission in 5 - Flare frequency: Before IFX treatment: 7.43±1.72/year (mean ± SD) During IFX treatment: 2.86 ± 1.90/year During 1st year after IFX withdrawal: 0.57 ± 0.43/year >12 months after IFX withdrawal: 0.13 ± 0.10/year - Long-term remission >12 months: 5 patients (72%)	- No deterioration in extraocular symptoms in any of patients after IFX withdrawal -Percentage of eyes with VA ≥ 0.5: ↑ from 39% at baseline to 54%. - 5 out of 6 eyes with VA ≤ 0.1 had macular degeneration and/or optic atrophy before IFX and did not improve. -AEs after IFX withdrawal > 12 months: 3 patients
Köse, 2020 [15]	-IFX 5 mg/kg at weeks 0, 2 and 6 and then every 4 weeks After 6 months of inactivity, ↓ to every 6 weeks. After a further 6 months of inactivity, ↓ to every 8 weeks. After 12 months of remission, withdrawn completely -AZA 2 mg/kg/d	- Flare frequency/year: Before IFX treatment: 4.8 ± 2.5 During IFX treatment: 1.3 ± 0.7. During 1st year after withdrawal: 0.77 ± 0.26. During 2nd year after withdrawal: 0.65 ± 0.34. -Sustained remission in 4 patients (50%), for 47 ± 30 months (range 12−90)	- Recurrence in 4 patients (50%), 2 while on IFN alpha-2a (25%) and 2 while on ADA, following the protocol for uveitis (25%) - Flare-free survival: 9 ± 8 months (range 2−18) -VA remained stable, except during flares -no changes on OCT during follow-up
Martin-Varillas, 2021 [16]	- 3−5 mg/kg iv bolus of IFX at weeks 0, 2 and 6, and then every 4−8 weeks until clinical remission for > 3 months. Shared decision-making with the patient, and treatment optimised by extending the dosing interval and/or reducing the dose	-Remission, defined as no signs of inflammation for ≥ 3 m, in 78 patients (77%) after a mean of 31.5 months on IFX - Treatment optimised in 18 patients. Mean OCT macular thickness decreased from 304±23 μm at baseline to 277±35 μm at the most recent visit. Reduction in retinal vasculitis (44% at baseline, 0% during optimisation, 0% at the end of follow-up). -Treatment not optimised in 42 patients - Improvement also observed in all ocular outcome measures in the non-optimised group. Hence, results were similar in patients with optimised and non-optimised treatment after mean follow-ups of 47 ± 18 and 28 ± 25 months respectively. - Improvement in anterior chamber cell grade in 18/18 vs 39/42 (100% vs 96%, $p = 0.99$), improvement in uveitis in 18/18 vs 31/42 (100% vs 74%, $p = 0.07$) and absence of retinal vasculitis in 18/18 vs 42/42 (100% vs 100%)	- Treatment regimen: 3 mg/kg/8 weeks in $n = 2$, 3 mg/kg/10 weeks in $n = 4$, 5 mg/kg/10 weeks in $n = 6$, and 5 mg/kg/12 weeks in $n = 6$; Completely withdrawn in $n = 6$. - Rates of recurrence, defined as a new flare in a patient in remission, very similar in optimised and non-optimised groups: median 0 (0−1) vs 0 (0−2), $p = 0.85$ - Immunosuppression scores in optimised and non-optimised groups: 11 (8−14) vs 8 (6−12) respectively, $p = 0.06$ - No serious AEs in optimised group. 3 cases of infusion-related skin reaction (7%), requiring treatment withdrawal, in patients with non-optimised treatment. - Costs of optimised and non-optimised treatment: €4827 vs €9854, i.e., annual costs 51% lower in optimised group.
Park, 2016 [17]	AS in remission after ETN ≥ 1 year and follow-up ≥ 6 months after dose reduction. Dose maintained in one arm and reduced in the other. Treatment regimen: 50 mg weekly (dose reduction or dosing interval extension allowed), then 25 mg weekly if patients remained in remission ≥ 6−12 m. Temporary interruption of treatment or dose ↑ allowed. Interruption> 3 months considered withdrawal.	-Remission: BASDAI<4, C-reactive protein < 0.5 mg/dL -Median time from ETN initiation to dose reduction: 20 weeks (25); in most cases (91%), reduction was gradual over 1 year - Drug survival longer in low-dose group in all time periods assessed, after adjusting for clinical factors. Adjusted HR=0.472, 95% CI 0.155−1.435, $p = 0.186$ - Survival positively correlated with time to dose reduction ($r = 0.261$, $p = 0.009$)	- Discontinuation due to AEs or lack of effectiveness in 22 patients (22%) in low-dose group vs 6 patients (17.6%) in standard-dose group - Reason for discontinuation: clinically relevant AE in 21/28 (75%) vs lack of effectiveness in 7/28 (25%). - Incidence of uveitis: 13 (9−16) per 100 patient−years on low doses vs 9 (4−18) on standard dose, p 0.423. Clinically relevant uveitis: 2.3 per 100 patient−years on low doses vs 3.1 on standard dose, $p = 0.625$
Shakoor, 2014 [18]	Uveitis in remission without GCs after IFX treatment, IFX tapered/stopped and flare-free survival assessed. Continuation of treatment with MTX or MMF was allowed.	Reasons for discontinuation: -Remission: 50% -AEs: 17% -Pregnancy: 11% -Poor adherence: 11% -Difficulties with administration: 6% -Unknown: 6% -Mean age at discontinuation: 20 years (13−35). Mean duration of uveitis: 4 years (3−10). Mean time on IFX 1 year (0.7−2.4). Significantly longer mean flare-free survival in 12 patients achieving GC-sparing inflammation control (doses ↓ ≤ 10 mg daily pred) within < 180 days - Mean age of patients with relapse: 19 (16−33) vs 29 (10−35, $p = 0.62$). amongst these patients, 6 (55%) were blind (VA <20/200) at presentation vs 2 of the patients without relapse (29%, $p = 0.37$)	Relapse in 11 patients (61%), 3 on MTX, 3 on MMF, and 5 not on any DMARDs -Mean flare-free survival: 603 days (95%, CI:8−1461), 7 cases (64%) of relapse occurring < 90 days after discontinuation and 8 (73%) within 1 year No relapse in 7 patients; of these, 2 later stopped MMF, 1 stopped MTX, 1 stayed on MTX and 1 on MMF, and 2 were not on DMARDs

(*continued*)

Table 2 (*Continued*)

Study	Optimisation or other procedure	Efficacy	Safety
Martín-Varillas, 2018 [19]	-ADA 40 mg fortnightly. After remission with ADA, shared decision-making between the patient and the physician, and treatment optimised by extending dosing interval: initially every 3 weeks and then every 4, 6 and 8 weeks until withdrawal after ≥ 24 months	-Remission, defined as no signs of inflammation for ≥ 3 m - VA significantly better in optimised group ($p<0.01$), and remain stable through optimisation until the end of follow-up. -Improvement also observed in ocular abnormalities in non-optimised group. Hence, most ocular outcomes were similar in optimised and non-optimised groups, after mean follow-ups of 35±13 and 26±22 months respectively since starting BT - ADA dosing intervals, at the most recent appointment, in the optimised group: Every 3 weeks in $n = 6$, Every 4 weeks in $n = 10$, Every 5 weeks in $n = 1$, and Every 8 weeks in $n = 2$; Completely withdrawn in $n = 4$. - No recurrence in the 4 patients in whom ADA successfully withdrawn, after a follow-up of 20±7 months after withdrawal	Recurrence, defined as a new flare in a patient in remission -in optimised group: 2 patients (monitored and ADA escalated to twice weekly) -in non-optimised group: 4 patients (monitored and 2 switched to IFX and 2 to golimumab) -OCT findings not significantly different between groups at the end of follow-up -Pred doses fell significantly in both groups -AEs in only non-optimised group (lymphoma, pneumonia, severe local reaction, bacteraemia due to *E. coli*). Costs lower in the optimised group Efficacy was similar but optimisation is safer and more cost-effective

Abbreviations: ADA: Adalimumab; BT: biological therapy; d: days; ETN: etanercept; GC: glucocorticoid; IFN: interferon; IFX: Infliximab; MNI: mean number of infusions of IFX before withdrawal; MMF: mycophenolate mofetil; MTX: methotrexate; AE: adverse event.

on initial clinical response. After increasing the ETN dosing interval, one patient who had been in remission developed uveitis that remained active despite returning to the initial dosage. Additionally, there was one case of uveitis amongst patients who showed a partial response to the BT but were not in remission.

In the cohort of Kawaguchi [14], TNF inhibitor discontinuation did not follow an established protocol, rather it was the consequence of various different events (pneumonia, tuberculosis, leukopaenia, lack of efficacy, psoriasis, liver dysfunction, and infusion reaction). Two patients had relapses while on IFX. The BT could only be discontinued in seven patients; of these, five (71%) experienced long-lasting remission (>12 months), while the other two had flares, although less frequently than at the initiation of the BT. Although VA improved from baseline, it remained very poor in some cases due to irreversible deterioration of vision having occurred before the IFX therapy.

Köse [15] proposed treatment optimization after 6 months of remission on IFX, consisting of two dose reductions at an interval of 6 months if remission was maintained. That is, the BT was discontinued if remission was sustained for 12 months. DMARDs were continued. These authors observed reductions in flares both during IFX therapy and for 1–2 years after its withdrawal. In half of the patients (n=4), remission was maintained for 47±30 months (range 12–90); in the other half, flares were observed, these being treated with IFN alpha-2a in two cases and ADA (at doses approved for uveitis) in the other two. The mean flare-free survival was 9±8 months (range 2–18).

Recently, Martín-Varillas et al. [16] have reported a multicentre prospective study involving 35 Spanish multidisciplinary units that followed up a cohort of 103 patients with refractory Behçet uveitis who had been treated with IFX for at least 24 months and in remission for at least 3 months. The BT was optimised by agreement between the patient and the physician, extending the interval between doses or progressively reducing the doses until complete withdrawal. Comparisons were made with patients in the same cohort in whom doses and dosing intervals were maintained. The IFX regimen was optimised in 18 cases and maintained in 42. The authors reported improvements in outcomes in both groups. There were no AEs amongst patients whose therapy was optimised, while such events were observed in those who remained on the initial regimen. Further, medication costs fell, annual costs being 51% lower in the optimised group.

Park [17] analysed 134 patients with AS in remission for at least 6 months, after 1 year of treatment with ETM (50 mg weekly), in whom dose reductions or dosing interval extensions were allowed at the physician's discretion. amongst patients meeting the same inclusion criteria, comparisons were made between those in whom optimisation was and was not attempted. Drug survival was longer in the optimised group in all the periods studied and after adjusting for clinical characteristics. The survival was positively correlated with time to dose reduction (r=0.261, p=0.009). Treatment discontinuation was due to a severe AE in 75% of cases and lack of effectiveness in the other 25%, with discontinuation rates of 22% and 17.6% in the optimised and standard-dose groups, respectively. The incidence of uveitis flares was in 13 (9–16) vs 9 (4–8) per 100 patient–years in the optimised and non-optimised groups respectively (p=0.423).

Shakoor [18] followed the course of 18 patients with uveitis in remission without glucocorticoids after treatment with IFX. The BT was tapered/stopped and patients were monitored until relapse. The objective was to assess relapse after the discontinuation of IFX. Patients were allowed to continue taking DMARDs. In half of the patients, the treatment was discontinued due to remission. Relapse occurred in 61% of cases, in a mean of 2 years.

The group of Martín-Varillas [19] also conducted an earlier multicentre prospective study in 35 Spanish multidisciplinary units following a cohort of 65 patients with refractory Behçet uveitis who had been treated with ADA (40 mg fortnightly) at least for 1 year and in remission for at least 3–6 months. Their BT was optimised by agreement between the patient and the physician, by extending the dosing interval until complete withdrawal. Data were compared with patients in the same cohort who opted to maintain the dose. Eye defects improved in both groups, but VA remained significantly better in those with optimised treatment ($p<0.01$). There were two cases of relapse in the optimised group, controlled in both cases by reducing the ADA dosing interval to fortnightly. There were four cases of relapse in the non-optimised group, which were control by switching treatments (two patients to IFX and two to golimumab). No relapses were observed in the four patients in whom ADA was completely withdrawn. AEs were only observed in the non-optimised group. Further, medication costs were lower in the optimised group.

Discussion

The role of TNF inhibitors and their efficacy in the treatment of NIU have been well established. Nonetheless, little is known regarding optimisation of this treatment or patients' clinical course after

optimisation, including whether drug-free remission is sustained. It is unclear the ideal moment to optimise or how long uveitis should be in remission with BT before optimisation and whether this time differs between the molecules used. The type of disease may also be a relevant factor, as some conditions are characterised by disease activity-free intervals.

Successful optimisation, and occasionally, sustained remission after complete withdrawal of TNF inhibitors have been described for conditions such as inflammatory bowel disease in patients with rheumatoid arthritis, psoriatic arthritis or psoriasis [5,20,21]. There is however a paucity of data in the literature on the clinical course of uveitis with BT and there is currently no consensus on when optimisation of this treatment should be attempted. While the studies analysed suggest that optimisation could be considered once uveitis has been in remission for 3 and especially 6 months, we believe that, as it is a potentially serious disease, remission lasting at least 6–12 months seems more appropriate. In relation to this, similar recommendations have already been made for other diseases treated with the same BTs [21].

Regarding the duration of remission after treatment discontinuation, Adán [9] reported drug-free remission of around 7.5 months, while Martín-Varillas [19] and Al Rashidi [10] reported periods of as long as 20 and 24 months, respectively. The earlier studies of Niccoli [22] and Doycheva [23] also found periods of up to 24 months. Therefore, BT optimisation seems to be an effective strategy in the long term in the majority of the cases described.

On the other hand, the percentage of patients who achieve long-term drug-free remission was 26% in Al Rashidi [10], while Kawaguchi [14] and Shakoor [18] reported rates of 72% and 50%, respectively, and the earlier study of Niccoli [22], a rate of 75%. These figures should be interpreted with caution, however, given the very small numbers of patients included in the studies; the rates might well be different in future larger studies.

As for the discontinuation of other treatments, Al Rashidi [10] reported discontinuation rates of 74% for glucocorticoids and even 40% for DMARDs. Similar data have been described with IFX in patients with Behçet disease [24,25].

Regarding uveitis relapse, Adán et al. [9] observed relapse in 50% of cases (2 patients), Al Rashidi [10] in 44% (4 patients), Breitbach [11] in 40% (8 patients), De Simone [12] in 25% (1 patient on IFN and 4 on IFX), Köse [15] in 50% (4 patients) and Shakoor [18] in 61% (11 patients), while De Stefano et al. [13] observed that 53% of patients showed either recurrence or AEs. Hence, the likelihood of relapse seems very variable, with rates generally ranging from 25% to 61%. Martín-Varillas et al. [19] observed an incidence of uveitis of 2 per 100 patient years in patients on optimised ADA treatment vs 4 per 100 patient years in those on non-optimised treatment; the difference between groups did not reach significance and there were no relapses amongst patients who discontinued the treatment. In their study on IFX [16], this group did not observe statistically significant differences between the groups and the mean relapse rate was nearly zero. Park et al. [17] reported an incidence of uveitis flares of 13 per 100 person-years amongst patients on low doses vs 9 per 100 person-years amongst those on the standard dose.

Reviewing the literature, Simonini et al. [26] found that, amongst patients in remission after BT, the time to first flare was significantly longer when ADA is used as the first biological rather than IFX, though optimisation of the BT was not attempted. In studies focused on ETN (De Stefano and Park [13,17]), uveitis flares occurred in both standard and low-dose groups. Some data in the literature suggest better control of ocular disease with IFX and ADA than with ETN [27].

Our findings are limited by the fact that they are based on studies with relatively small numbers of cases, many of which did not have a control group or were retrospective. There is great variability in terms of when optimisation is attempted. Further, protocols differ markedly, and in many cases, there is no tapering strategy, but rather direct withdrawal, this being associated with disease reactivation in a relatively high percentage of cases. Data on the outcomes of interest were also not homogeneous. The lack of homogenous scientific data meant that we were unable to perform other types of analysis, such as the calculation of confidence intervals.

Despite all this, our results suggest that it is possible to optimise and/or completely withdraw (in selected cases) TNF inhibitor BTs in a safe and planned way, with relapse occurring in between a quarter and two-thirds of cases. In the event of uveitis reactivation, it seems that the disease can be brought back under control in most cases, by re-escalating to the standard doses of each medication, and in a small percentage of cases, by switching to another BT.

No major safety issues were reported in any of the studies analysed. While our findings do mitigate some concerns, they also highlight that, in the field of uveitis, we should make greater efforts to collect more homogeneous data, to facilitate future comparisons. There is a need for further studies that include larger samples of patients treated following established protocols using uniform

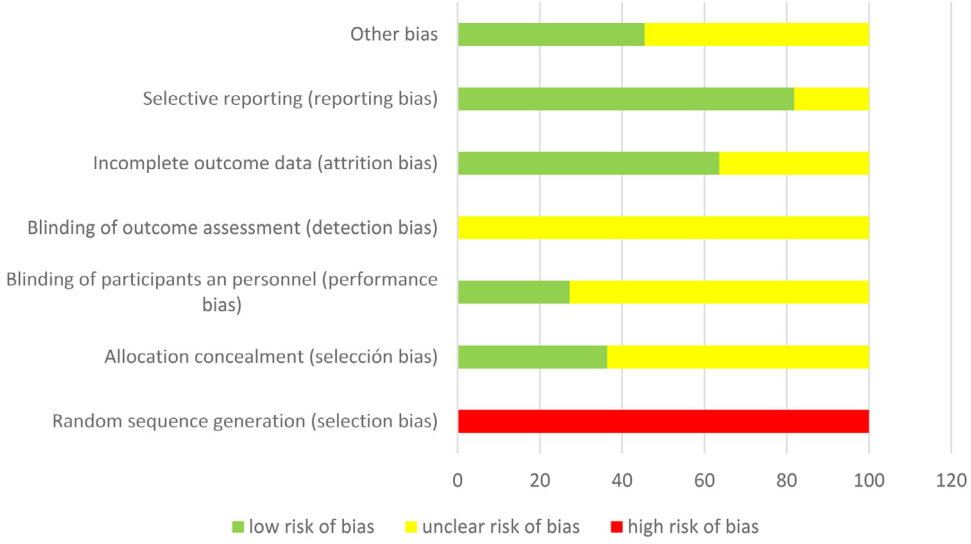

Fig. 2. Risk of bias graph.

criteria, to determine the ideal duration of treatment and whether the success of optimisation/withdrawal of BTs differs depending on the cause of the uveitis and the biological used.

According to the evaluation of all potential biases, with the ROBINS-1 tool, allows classifying most of the studies with serious risk and some with moderate risk (Table 1,Fig. 2, Supplementary table S6). After the systematic review of the literature, a small number of articles were obtained that performed optimization of biological therapy. Therefore, we have incorporated all the articles retrieved in this review, despite the fact that some did not present a control group.

The inclusion of descriptive observational studies (case series) with and without a control group may compromise the results of a systematic review, due to the low level of evidence they provide and may not allow a meta-analysis to be carried out. But we think that in this case, it can be a starting point to know the deficiencies that exist published in the field of uveitis. We want to avoid a publication bias, because this article shows that in the field of uveitis, there are some gaps in the methodology and systematics used in the publications and that we would have to modify to favour future comparative studies.

In conclusion, the studies included generally provide poor quality evidence. There is great variability between the studies in design, number of patients included (though most have small sample sizes), underlying disease, type of uveitis, definitions and outcome variables. The criteria applied (clinical, chronological, etc.) to decide when to optimise the treatment were not uniform, indicating a lack of consensus on the initiation of biological therapy optimisation. A standardised optimisation regimen/protocol has yet to be established. The likelihood of relapse after optimisation is variable. In the event of reactivation, remission is achieved again by returning to the previous dosing schedule in the majority of cases.

We describe a series of articles where an optimization of biological therapy (with TNF inhibitors) has been applied in patients with non-infectious uveitis in remission. Due to the results achieved with the systematic review, no evidence on the efficacy and safety of optimization can be concluded. Although the data reviewed suggests a trend that would support it, it will need to be confirmed in future studies. We can indicate that the methodological quality of the included studies is low. No clinically relevant safety issues have been identified. And more high-quality uveitis-specific studies are needed, including more patients with uniform criteria, including different diseases and different BTs (including all TNF inhibitors but also biologics targeting non-TNF targets).

Funding

No specific funding has been received from any public, private or non-profit organisations to perform the review and analysis of the evidence described in this paper.

Declaration of Competing Interest

The authors have no conflicts of interest to report in relation to this review.

Registration

The protocol for the systematic review of the literature designed for this study was registered with PROSPERO (registration number 236,852).

Acknowledgments

The authors would like to thank the Spanish Rheumatology Society for their support for the publication of this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.11.010.

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