The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease: results of a multicentre open-label study

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ABSTRACT

Objective. *To assess the efficacy of other biologic therapies, different from IFX and ADA, in patients with Behçet's disease uveitis (BU).*

Methods. *Multicentre study of 124 patients with BU refractory to at least one standard immunosuppressive agent that required IFX or ADA therapy. Patients who had to be switched to another biologic agent due to inefficacy or intolerance to IFX or ADA or patient´s decision were assessed. The main outcome measures were the degree of anterior and posterior chamber inflammation and macular thickness.*

Results. *Seven (5.6%) of 124 cases (4 women/3 men; mean age, 43 (range 28-67) years; 12 affected eyes) were studied. Five of them had been initially treated with ADA and 2 with IFX. The other biologic agents used were golimumab (n=4), tocilizumab (n=2) and rituximab (n=1). The ocular pattern was panuveitis (n=4) or posterior uveitis (n=3). Uveitis was bilateral in 5 patients (71.4%). At baseline, anterior chamber and vitreous inflammation were present in 6 (50%) and 7 (58.3%) of the eyes. All the patients (12 eyes) had macular thickening (OCT>250μm) and 4 of them (7 eyes), cystoid macular oedema (OCT>300 μm). Besides reduction anterior chamber and vitreous inflammation, we observed a reduction of OCT values, from 330.4±58.5 μm at the onset of the biological agent to 273±50 μm at month 12 (p=0.06). Six patients achieved a complete remission of uveitis.*

Conclusion. *The vast majority of patients with BU refractory to standard immunosuppressive drugs are successfully controlled with ADA and/or IFX. Other biologic agents also appear to be useful.*

Introduction

Behçet's disease (BD) is an idiopathic, chronic-relapsing systemic vasculitis mainly characterised by the presence of recurrent oral and genital aphthous ulcers, skin lesions and ocular involvement (1, 2). Eye is affected in 50–70% of patients, and Behçet's uveitis (BU) represents one of the leading causes of blindness worldwide (3-4). Therefore, a rapid and aggressive treatment is crucial to avoid this complication. With the use of traditional immunosuppressive drugs such as azathioprine (AZA) or cyclosporine A (CsA) (5-6), the percentage of patients with vision loss or severe ocular sequelae has considerably decreased. Nevertheless, during the last years, several studies have shown that notwithstanding the use of immunosuppressive drugs, a loss of vision occurs in up to 74% of affected eyes within 5 to 10 years of the onset of the disease (1, 3, 7-8).

The recent use of biologic agents to treat BU has substantially improved the prognosis of this disease. Tumour necrosis factor (TNF)-α inhibitors, mainly infliximab (IFX) and adalimumab (ADA), have been the most commonly studied biologic drugs for uveitis (9-17). Moreover, according to the "Expert panel recommendations for the use of anti-TNF biologic agents in patients with ocular inflammatory disorders" (18), IFX and ADA should be considered as a second or even first line corticosteroid-sparing treatment in patients with BU. In this regard, we have recently reported a large series of patients with refractory BU treated with IFX or ADA (19).

Although the use of these anti-TNF-α agents yielded a significant improvement, in some patients, IFX and ADA were unable to control intraocular inflammation or had to be withdrawn due

to adverse effects. These patients constitute a challenge for the clinicians, and other anti-TNF-α drugs have been tested in this scenario (20-21). Moreover, there are small case series or case reports assessing the efficacy of biologic drugs different from IFX or ADA (22-26).

Taking into account these considerations, we aimed to determine the efficacy of other biologic agents different from IFX or ADA in a series of patients with BU who had to be switched to another biologic agent due to inefficacy of IFX or ADA, intolerance to these biologic agents or patient's preference.

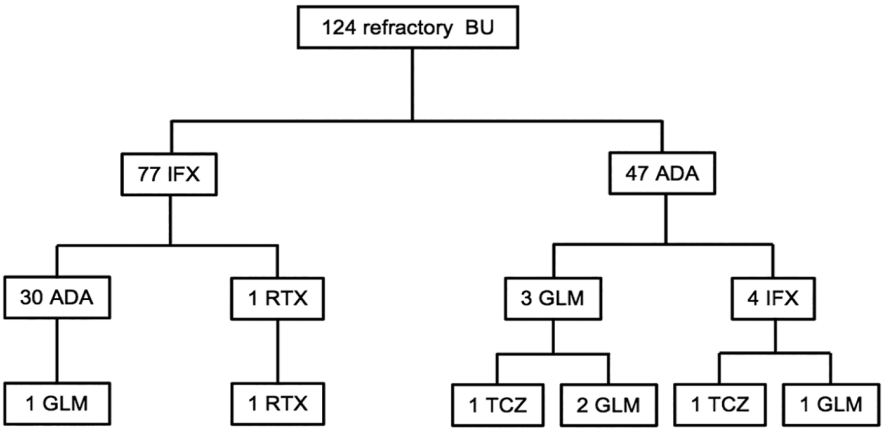

Fig. 1. Flow-chart of 124 patients with refractory Behçet's uveitis to standard synthetic immunosuppressive drug that required biologic therapy.
BU: Behçet uveítis; IFX: infliximab; ADA: adalimumab; RTX: rituximab; GLM: golimumab; TCZ: tocilizumab.

Patients and methods

Design and enrolment criteria

We set up an interventional case series, open-label, multicentre study of patients with refractory BU. They were studied at the "Uveitis Units" of 38 referral centres from Spain. The initial sample included 124 patients with BU refractory to at least one systemic traditional immunosuppressive drug. Of them, we focused on those who received a biologic agent different from IFX or ADA (Fig. 1).

Methods have been previously published (19). Briefly, BD was diagnosed according to the proposed International Criteria (27). Uveitis was classified anatomically, according to the International Uveitis Study Group (IUSG) classification (28).

Patients treated with biologic agents different from IFX or ADA due to inadequate response, inefficacy or toxicity to IFX or ADA or those in whom biologic agents different from IFX and ADA were used due to patient preference for a different administration route or frequency were assessed in the present study.

Inefficacy to these biologic agents was considered to be present in cases of uveitis with uncontrolled intraocular inflammation or when the patient did not reach enough clinical improvement after receiving a 6-week course of intravenous IFX (5 mg/kg/6 weeks) and/or subcutaneous ADA (40 mg/kg/2 weeks) (29). We considered "enough improvement" when the patient fulfilled The Standardisation of Uveitis Nomenclature (SUN) Working Group criteria, that is, grade zero inflammatory activity in the anterior chamber and/or in the vitreous, during a 6-week period. Moreover, grade zero should be reached in less than 3 months, or it would be just considered as a partial response (30).

Exclusion criteria were as follows: recent serious, recurrent or chronic infection, (including human immunodeficiency virus infection, hepatitis B or C virus infection or tuberculosis); liver, renal, heart, or demyelinating disease; history of substance abuse; malignancy or solid-organ transplantation; and intraocular surgery in the previous 3 months.

Since biologic therapy is an off-label indication for uveitis, written informed consent was requested and obtained in all the patients. A minimum period of 12 months of follow-up since the first biologic agent onset was required to be included in the study.

According to the national guidelines, latent tuberculosis was excluded by a tuberculin skin testing, and/or serum quantiferon test, as well as a chest radiograph. In patients with latent tuberculosis, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic agent, and maintained for 9 months.

Outcome variables and working definitions

Intraocular inflammation, macular thickness and visual acuity were considered as the outcome variables. They were recorded in most patients at baseline and at week 1, and months 1, 3, 6 and 12. They were assessed according to a standardised follow-up protocol agreed beforehand in each centre.

Intraocular inflammation

The degree of intraocular inflammation was evaluated according to the SUN Working Group recommendations (30). Nussenblat scale was used to assess the degree of vitritis (31). Fluorescein angiogram (FA) was performed routinely before and after the onset of the biologic agent, to determine the presence or absence of retinal angiographic leakage. FA was reviewed for the presence or absence of vasculitis, papillitis and cystoid macular edema (CME). Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on FA (3). Choroiditis and retinitis were considered active or inactive depending on the presence or absence of activity signs on the ophthalmoscopic examination and/or FA.

Macular thickness

Macular thickness was measured by optical coherence tomography (HD-OCT). All the scans were performed using Cirrus HD-OCT (Carl Zeiss, Ca, USA) and obtained by the 512x128 scan Pattern. Macular thickening was defined as a macular thickness greater than 250 μm, whilst CME was considered when macular thickness was greater than 300 μm.

Visual acuity

The best-corrected visual acuity (BCVA)

was determined using the Snellen test. Obtained visual values were converted to logarithm of the minimum angle of resolution (logMAR) scores for statistical purposes.

A *relapse* was considered to be present whether a patient who was in remission experienced a new flare of uveitis (31). *Remission* was defined as inactive disease for at least 3 months after discontinuation of all treatment for eye manifestations (30).

Statistical analysis

Results were expressed as mean±SD or median [25^{th}-75^{th} interquartile range (IQR)] as appropriate. Continuous variables were compared by using the Wilcoxon signed-rank test. Comparisons of the outcome variables were performed at baseline and at week 1, and months 1, 6 and 12. STATISTICA software (StatSoft Inc. Tulsa, Oklahoma, USA) was used for the analysis. A level of $p<0.05$ was considered statistically significant in all the calculations.

Results

Baseline demographic and general data

Seven (4 women/3 men; 12 affected eyes) of 124 (5.6%) patients with BU initially treated with IFX or ADA were switched to another biologic agent (Table I). The mean age was 43±11 (range 28-67) years. HLA-B51 was positive in 5 (71.4%) of the 7 patients, and uveitis was bilateral in 5 cases.

Besides oral corticosteroids and before starting biologic therapy, patients had received the following treatments: methylprednisolone pulses (n=3), cyclosporine (n=7), methotrexate (n=4), and azathioprine (n=3). After the failure of these drugs, ADA (n=5) and IFX (n=2) were started. ADA had been used as monotherapy in 1 patient. In the remaining patients, the biologic therapy with IFX or ADA had been used in combination with synthetic immunosuppressive therapy: cyclosporine (n=4), methotrexate (n=1), and azathioprine (n=1) (Table I).

The median period from the diagnosis of BD to the onset of the first biologic drug (IFX or ADA) was 48 months (7-127).

Biologic therapy different from IFX or ADA

Biologic agents different from IFX or ADA were used in 7 of the 124 (5.6%) patients with severe BU due to the persistence of active uveitis (n=4), intolerance to ADA and IFX (n= 2) or patient preference for subcutaneous administration (n=1).

The management of these patients and the biologic agents used are shown in Figure 2. They were specifically, GLM (n=4), TCZ (n=2), and RTX (n=1).

Clinical efficacy of biologic therapy different from IFX or ADA

As stated above, intraocular inflammation, macular thickness and visual acuity, were the outcome variables assessed in this study. Following the use of these biologic agents improvement in inflammation of the anterior chamber, vitritis, diffuse capillary leakage and macular thickness was achieved (Fig. 3). Three patients experienced a decrease in the number of anterior chamber cells and 4 patients had improvement of vitritis after 3 months of treatment and almost complete resolution of the inflammatory process after one year. The mean BCVA increased from 0.71±0.24 before the onset of the new biologic agent to 0.92±0.13 at month 3 (p=0.03). Concerning OCT, we observed that, at the onset of the biologic therapy different from IFX or ADA, all the patients (12 eyes) had macular thickening (OCT>250 μm) and 4 (7 eyes), CME (OCT>300 μm). The mean OCT decreased from 330±58 microns, at baseline, to 273±50 μm at 12 months (p=0.067).

Follow-up and side-effects of biologic therapy different from IFX or ADA

After 1 year of follow-up, complete clinical control of ocular inflammation was achieved in all the patients. Thereafter, GLM was discontinued in 1 patient because of complete resolution of uveitis after 6 months of therapy.

Biologic therapy was well tolerated in all patients throughout the follow-up period (overall, 48 (36-66) months; 12 (7-42) months after switching from IFX or ADA to other biologic agent). None of these patients required the withdrawal of the new biologic drug.

Table I. Baseline clinical and ophthalmological features of 7 patients with Behçet's uveitis undergoing biologic therapy.

Mean age ± SD (years)	n
Sex (men/women)	3/4
HLA-B51 positive	5
Number of affected eyes	12
Pattern of uveitis	
Bilateral/unilateral	5/2
Posterior	3
Panuveitis	4
Previous treatment	
CsA	7
MTX	4
AZA	3
Bolus of methylprednisolone i.v.	3
Initial biologic therapy	
IFX	2
ADA	5
Monotherapy/combined treatment	1/6

Abbreviations: CsA: cyclosporine A; AZA: azathioprine; MTX: methotrexate; IFX: infliximab; ADA: adalimumab.

Discussion

Ocular involvement in BD is a frequent and severe complication that may determine an irreversible structural damage, leading to visual loss. The percentage of patients with vision impairment varies upon the series, but it remains unacceptably high despite the use of conventional systemic immunosuppressive drugs (1, 3, 8).

With the advent of biologic therapy, the prognosis of refractory or severe uveitis has undergone a radical change. The efficacy of the biologic therapy has been supported by several studies. In this regard, IFX and ADA have been the most commonly studied agents in BU, showing promising results (9, 16, 32-34).

Based on the results derived from our previous study on 124 patients with BU (19), we confirmed that almost 95% of patients with BU refractory to conventional immunosuppressive drugs are successfully treated with IFX or ADA. However, the management of BU with inadequate response to these two biologic agents remains as an important challenge for the clinician. In this sense, there are only a few case reports discussing the use of other biologic therapies in patients with refractory BU, in particular (22-26), or with refractory

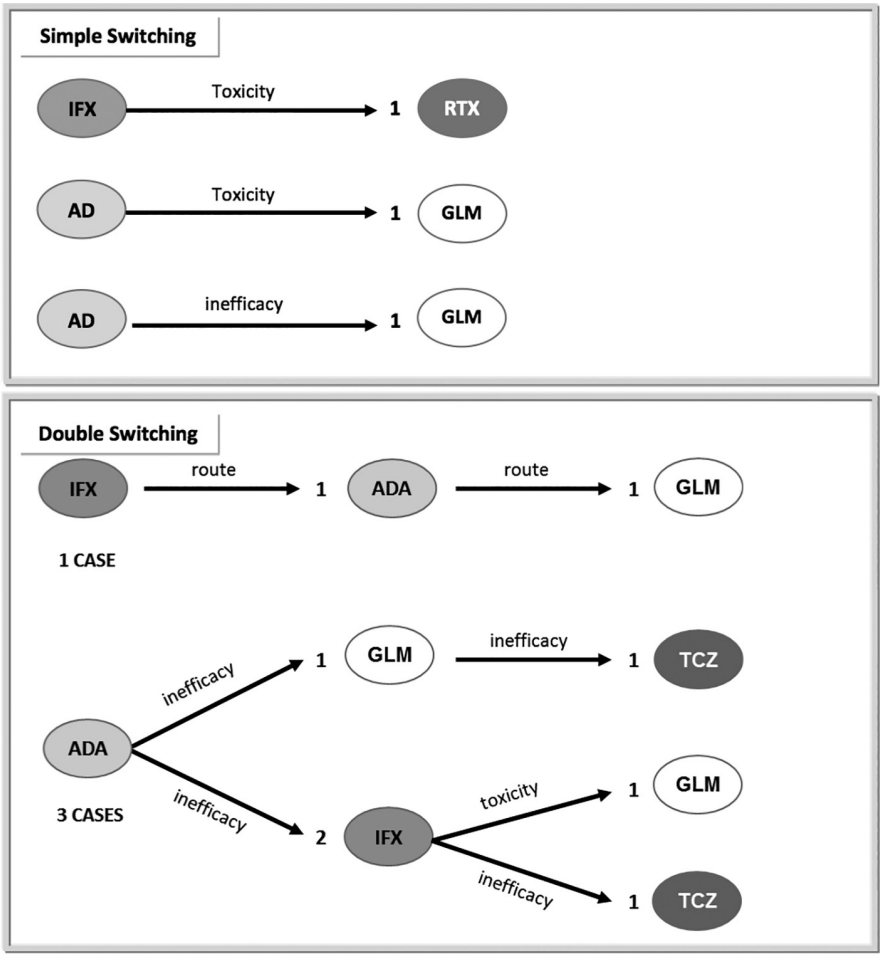

Fig. 2. Reasons for switching the standard biologic immunosuppressive drug (IFX or ADA) to another biologic agent in 7 patients with refractory BU.
IFX: infliximab; ADA: adalimumab; GLM: golimumab; TCZ: tocilizumab; RTX: rituximab; BU: Behçet uveitis.

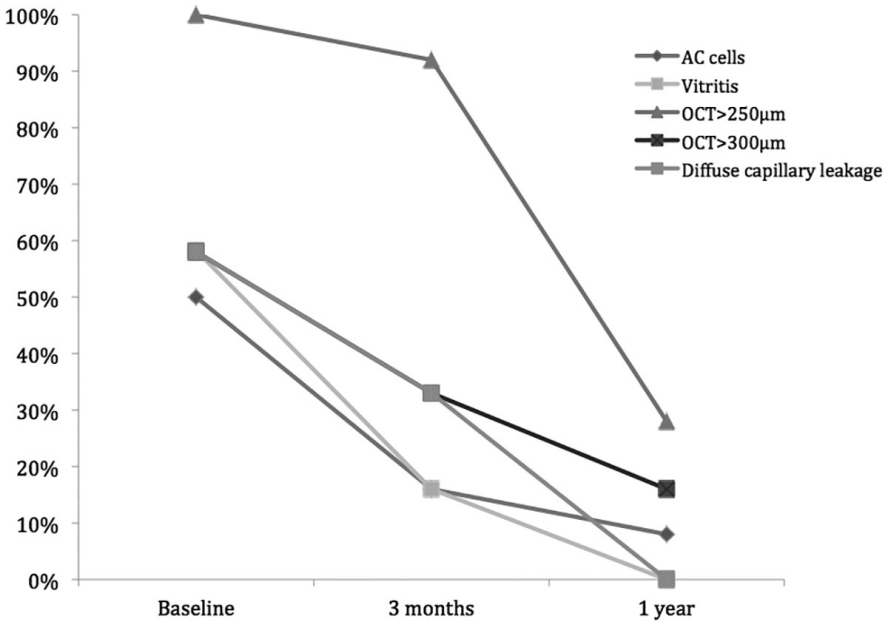

Fig. 3. Rapid and maintained improvement following the onset of a biologic therapy different from IFX or ADA on anterior chamber cells (AC cells) vitritis, diffuse capillary leakage and macular thickness after 3 and 12 months of treatment. (Data expressed as percentage of affected eyes).

uveitis, in general (35-40). In patients with refractory BU, the reported biologic treatment has been GLM (3 cases) (22, 23), RTX (1 case report and a pilot study in 20 patients with BU) (24-25, 41) or TCZ (5 cases) (26, 41-45).

To further investigate this issue, we assessed 124 patients from a multicentre study with refractory BU initially treated with IFX or ADA. In our series, only 7 patients required switching to a biologic agent different from IFX or ADA. In this regard, GLM was used in 4 patients, TCZ in 2 and RTX in 1 patient.

GLM is a fully humanised monoclonal antibody against TNF-α, with a recommended dose of 50 mg by subcutaneous injection every month. To our knowledge, the use of GLM in BU was only described in a case report (22) and in two patients from a case series (23). Nevertheless, our results, specifically on inflammation and macular thickness, might support the potential use of this biologic agent in patients with refractory BU.

On the other hand, TCZ is an anti-IL-6 receptor monoclonal antibody. Recommended doses vary from 4 to 12 mg/kg every 2-4 weeks, administered as an intravenous infusion. In keeping with the case report published of BU (26), we used the dose of 8 mg/kg/4 weeks in the two patients included in our series. In both cases, complete remission of BU was achieved.

RTX is a chimeric mouse-human IgG1 antiCD20 monoclonal antibody given by intravenous infusions in various doses depending on the diagnosis. The cases of BU treated with RTX that, to our knowledge are published in the literature, used two doses of 1 g every 2 weeks (24-25) with a good control of uveitis and retinal vasculitis. They are included in two studies; a case report, and a prospective trial on 20 patients randomised into two groups; the first one received RTX plus methotrexate and the second one, cyclophosphamide plus azathioprine. RTX-treated group had more substantial improvement of the Total Adjusted Disease Activity Index, whereas ocular inflammation improved significantly in both groups. We had a single patient with BU treated

with RTX in our series. Our patient was treated with 2 intravenous infusions of RTX at a dose of 1,000 mg (on days 1 and 15) every 6 months. The good response observed in our patient was in line with the information previously reported on this biologic agent.

Finally, certolizumab pegol is a Fab 'fragment of a humanised recombinant antibody against TNF-α and conjugated to polyethylene glycol. Although none of the patients from our series was treated with certolizumab, there are some studies suggesting that this agent may be an effective alternative in the treatment of refractory uveitis (46, 47).

Some authors have suggested withdrawing the biologic therapy in patients with persistent inactive ocular inflammation (17, 39-40). In this regard, we were able to do so in one patient treated with GLM, without uveitis reactivation. However, based on our small series, we cannot draw conclusions on this issue and more studies are needed to clarify this question.

Taking into account the growing number of biologic agents, several options are now available to treat uveitis with inadequate response to IFX or ADA, as we have already mentioned. This represents a clear advantage for the clinician, although the choice of the optimal agent still remains a difficult task. Considering the results of our study and all the results derived from the literature review, we herein propose a scheme of treatment for patients with BU (Fig. 4). Besides systemic corticosteroids, we propose that the first step in the management of BU must include the use of a conventional synthetic immunosuppressive agent, such as cyclosporine, azathioprine or mycophenolate. In those patients with persistent uveitis, or even as a first option in cases of severe uveitis, ADA or IFX should be initiated unless contraindicated (*e.g.* demyelinating disease, optic neuritis) (18). If adequate control of BU is not achieved, we will have to choose between a different anti-TNF-α drug or another class of biologic agent. To do so, we have to consider whether we are dealing with a primary failure (lack of response to the biologic drug from the beginning) or with a secondary failure (loss of efficacy after a primary response). In the first case, we propose to switch to a biologic drug with a different mechanism of action (tocilizumab, rituximab, or even abatacept). In the second case, the mechanism of the treatment failure could be the development of autoantibodies against the biologic drug, which is known as immunogenicity. The effects of these antibodies are unclear, but they may be associated with drug reactions and loss of efficacy over time. In these cases of secondary failure, several studies in patients with BU (488), and rheumatoid arthritis (49, 50) have shown that the use of a different anti-TNF-α drug (golimumab) yields similar efficacy to that of the first anti-TNF-α agent prescribed.

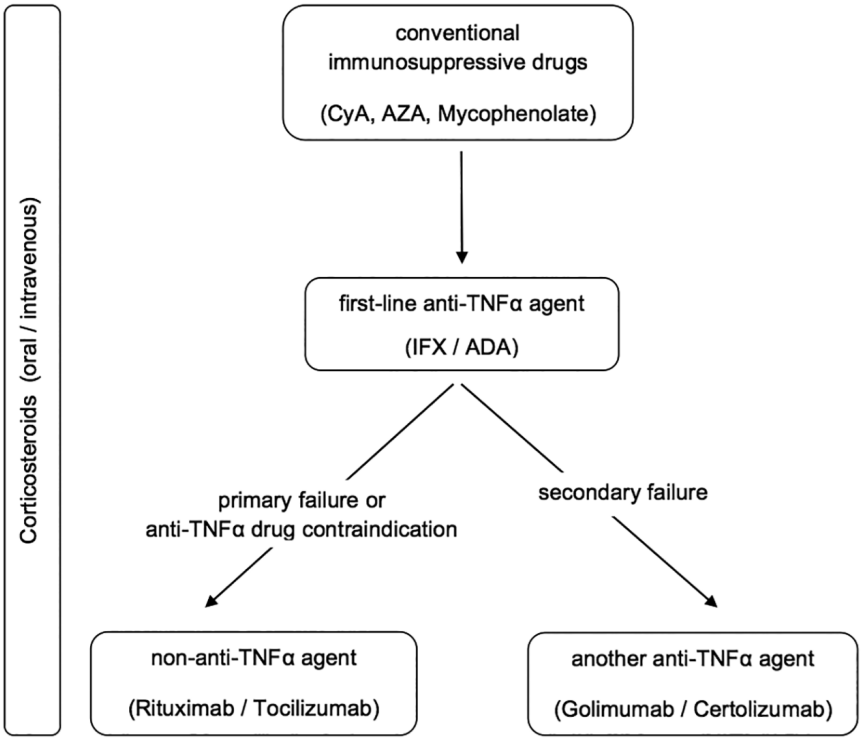

Fig. 4. Proposed therapeutic scheme for Behçet's uveitis.

Some studies suggest that anti-TNF-α monoclonal antibodies are more effective than the TNF soluble receptor (etanercept) for the treatment and prevention of uveitis (51). Paradoxically, in some cases TNF-α inhibitors, mainly etanercept, have been reported to cause uveitis (52).

Alpha interferon has proved to be a useful drug in the management of patients with uveitis secondary to BD (53). However, the use of interferon is often associated with some side effects such as fatigue. Due to this, in this multicentre study, in which took part several several units of uveitis of Spain, the agreed to use of anti-TNF-α in patients refractory to conventional immunosuppressive therapy (54-56).

Our study has the limitations derived from the small number of cases included. Nevertheless, it represents the largest series of BU patients with inadequate response to IFX and/or ADA. We believe that our results may help to improve the experience on the use of the new biologic agents in refractory BU, an infrequent but serious disease for which no strong therapeutic options are available to date. Indeed, large prospective studies are needed to confirm our results and also to assess the long-term efficacy and safety of these biologic agents different from IFX or ADA in patients with BU.

In conclusion, the vast majority of patients with BU who are refractory to standard immunosuppressive drugs are successfully controlled with ADA and/or IFX. Other biological agents appear to be also useful in BU refractory to these two agents.

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Competing interests

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