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Original article

Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients

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Abstract

Objective. The aim of this study was to assess the efficacy of anti-TNF-α therapy in refractory uveitis due to Behçet's disease (BD).

Methods. We performed a multicentre study of 124 patients with BD uveitis refractory to conventional treatment including high-dose corticosteroids and at least one standard immunosuppressive agent.

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CLINICAL SCIENCE

Patients were treated for at least 12 months with infliximab (IFX) (3–5 mg/kg at 0, 2 and 6 weeks and then every 4–8 weeks) or adalimumab (ADA) (usually 40 mg every 2 weeks). The main outcome measures were degree of anterior and posterior chamber inflammation, visual acuity, macular thickness and immunosuppression load.

Results. Sixty-eight men and 56 women (221 affected eyes) were studied. The mean age was 38.6 years (S.D. 10.4). HLA-B51 was positive in 66.1% of patients and uveitis was bilateral in 78.2%. IFX was the first biologic agent in 77 cases (62%) and ADA was first in 47 (38%). In most cases anti-TNF-α drugs were used in combination with conventional immunosuppressive drugs. At the onset of anti-TNF-α therapy, anterior chamber and vitreous inflammation was observed in 57% and 64.4% of patients, respectively. In both conditions the damage decreased significantly after 1 year. At baseline, 50 patients (80 eyes) had macular thickening [optical coherence tomography (OCT) >250 μm] and 35 (49 eyes) had cystoid macular oedema (OCT>300 μm) that improved from 420 μm (S.D. 119.5) at baseline to 271 μm (S.D. 45.6) at month 12 ($P < 0.01$). The best-corrected visual acuity and the suppression load also showed significant improvement. After 1 year of follow-up, 67.7% of patients were inactive. Biologic therapy was well tolerated in most cases.

Conclusion. Anti-TNF-α therapy is effective and relatively safe in refractory BD uveitis.

Key words: Behçet's disease, uveitis, anti-TNF therapy.

Introduction

Behçet's disease (BD) is an idiopathic, polysymptomatic, chronic, recurrent systemic vasculitis characterized mainly by the presence of recurrent oral aphthous ulcers, genital ulcers, skin lesions and ocular involvement [1]. The underlying pathology is an obliterative and necrotizing vasculitis that affects both the arteries and the veins of any size of any affected organ system [1]. BD is more frequent and severe in patients from the eastern Mediterranean countries and Asia [2], but is also seen in southern European regions. In north-western Spain the annual incidence rate was 0.66/100 000 [3]. This is higher than in other southern European regions, such as Reggio-Emilia, where the annual incidence is 0.24/100 000 [4].

BD is a leading cause of blindness [5]. The frequency of ocular involvement in patients with BD ranges from 50% to 70% [5–10]. The typical pattern of ocular involvement is a recurrent uveitis that may affect any segment of the uvea, from the anterior chamber to posterior, but it may present as a panuveitis [5]. Lesions affecting the posterior segment have a poorer prognosis since they are usually persistent, leading to severe vision loss [11]. The percentage of vision impairment in these cases varies between 25% and 70% [1, 5, 12–14].

Major advances in the management of uveitis have been described in the past three decades. It is also applicable to the uveitis associated with BD [5]. Since the introduction of immunosuppressive drugs such as AZA and ciclosporin A (CsA), the prognosis of visual loss in patients with BD has improved substantially. However, despite using these drugs, the number of BD patients who experience visual loss still remains inappropriately high [1, 5, 12–14]. Nevertheless, the advent of biologic therapies, in particular monoclonal antibodies directed against TNF-α, has contributed to the improvement of visual outcome in these patients.

Several studies have demonstrated the presence of high levels of TNF-α in the serum and aqueous humour of patients with uveitis [15–17]. Experts in the field highlight the beneficial effect of anti-TNF-α agents in the management of BD complications [18–20]. More specifically, anti-TNF-α agents, in particular infliximab (IFX) and adalimumab (ADA), have been successfully used in BD patients with uveitis refractory to conventional immunosuppressive therapy [21–30]. However, in most cases information related to this issue is based on small series or case reports [21, 29, 31–33].

Taking into account these considerations, our aim was to assess the clinical response to biologic therapy in a large series of BD patients with uveitis refractory to standard conventional synthetic immunosuppressive therapy.

Patients and methods

Design and enrolment criteria

We set up an interventional case series, open-label, multicentre study that included 124 patients with uveitis due to BD refractory to conventional immunosuppressive therapy. Patients were studied in outpatient clinics of the uveitis units of 38 referral centres from Spain.

The diagnosis of BD was performed according to the proposed International Criteria for BD [34]. Patients included in the present study also required the presence of uveitis with partial or no response to corticosteroids and at least one conventional immunosuppressive drug. As previously described, patients were defined as having refractory uveitis if intraocular inflammation was not controlled despite receiving prednisone (or equivalent) at doses required for clinical improvement (generally high

doses) and therapeutic doses of conventional immunosuppressive drugs or the use of these drugs was not able to keep the disease under control for a minimum of 1 year, defined as having a history of at least one relapse in the year before enrolment that required an increase in the dose of oral corticosteroids or other immunosuppressive agents [26].

Exclusion criteria were recent serious, recurrent or chronic infection, including HIV, HBV, HCV or tuberculosis (TB); liver, renal, cardiac or demyelinating disease; history of substance abuse, malignancy or solid-organ transplantation; or intraocular surgery in the previous 3 months.

This was an observational study of anti-TNF-α therapy in patients with refractory uveitis due to BD. In such studies, ethics committee approval is not mandatory according to Spanish national regulation. However, written informed consent is mandatory and was obtained from all patients.

For inclusion in the present study, it was required that all patients have at least 1 year of follow-up. Uveitis was classified anatomically according to the International Uveitis Study Group (IUSG) classification [35].

In all patients, latent TB was excluded by a tuberculin skin test [purified protein derivative (PPD)] and/or Quantiferon and chest radiograph because of the risk of reactivation with anti-TNF-α therapy. In those patients showing with previous history of TB, active infection was ruled out. In patients with latent TB, prophylaxis with isoniazid was initiated at least 3–4 weeks before the onset of biologic therapy. Overall, prophylaxis with this drug was maintained for 9 months.

Outcome variables

Intraocular inflammation, macular thickness, visual acuity, the sparing effect of corticosteroids and the immunosuppression load score were the outcome variables. These outcome variables were recorded in most patients at baseline and at 1 week, 1 month, 3 months, 6 months and 1 year. They were assessed according to a follow-up protocol agreed beforehand that was performed in each centre.

The degree of intraocular inflammation was evaluated according to the Standardization of Uveitis Nomenclature (SUN) Working Group [36]. The Nussenblat scale was used to evaluate the degree of vitritis [37].

Fluorescein angiography (FA) was performed routinely before and after the onset of treatment to determine the presence or absence of retinal angiographic leakage. FA results were reviewed for the presence or absence of vasculitis, papillitis and cystoid macular oedema (CME). Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on FA [5]. Choroiditis and retinitis were considered active or inactive depending on the presence or absence of activity data on ophthalmoscopic examination and/or FA.

Macular thickness was measured by optical coherence tomography (OCT). All high-definition OCT (HD-OCT) scans were performed using a Cirrus HD-OCT (Carl Zeiss, Dublin, CA, USA). Scans were obtained using the 512×128 scan pattern. Macular thickening was defined as a macular thickness $>250\,\mu$m, whereas CME was defined as a macular thickness $>300\,\mu$m.

The best-corrected visual acuity (BCVA) was determined using the Snellen test. Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) scores for statistical analysis.

The degree of immunosuppression was calculated according to the semi-quantitative scale proposed by Nussenblatt *et al*. [38]. The grading scheme provides a combined, single numerical score for the total immunosuppression load per unit of body weight per day. Grades for each agent (prednisone, ciclosporin, AZA, MTX and chlorambucil) ranged from 0 to 9, whereas MMF ranged from 0 to 7. For patients receiving multiple medications, the sum of the grading score for each drug was used to calculate the total immunosuppression score at the baseline visit and at each visit on a scale from 0 to 15. Topical or peri-ocular corticosteroid therapy was excluded from the calculation of the immunosuppressive load [26]. The dose of biologic agent was not used to calculate the final immunosuppressive load.

A relapse was considered to be present if a patient who was in remission experienced a new flare of uveitis [37]. Remission was defined as inactive disease for at least 3 months after discontinuation of all treatment for eye manifestations [36].

Statistical analysis

Statistical analysis was performed using STATISTICA software (StatSoft, Tulsa, OK, USA). The results were expressed as mean (S.D.) for variables with a normal distribution or as median [25th–75th interquartile range (IQR)] when they were not normally distributed. The comparison of continuous variables was performed using the Wilcoxon test.

The following variables were assessed: BCVA, anterior chamber cells, vitritis, choroiditis, retinitis, retinal vasculitis and OCT. Comparisons of these variables were made between baseline and 1 week, 1 month, 6 months and 1 year.

Results

Demographic and general data at baseline

A total of 124 patients (221 affected eyes) with uveitis refractory to conventional immunosuppressive therapy were studied (Table 1). Men slightly outnumbered women (68 men/56 women). The mean age was 38.6 years (S.D. 10.4; range 10–67). HLA-B51 was positive in 66.1% of patients. In most cases uveitis was bilateral (78.2%).

Besides oral corticosteroids [maximum prednisone daily dosage 100 mg/day, median 37.5 mg/day (IQR 30–60)] and before the onset of biologic therapy, patients had received the following medication: i.v. pulses of methylprednisolone (MP) (34 patients), CsA (102 cases), AZA (66 patients) and MTX (62 patients). The therapeutic schedule for pulses of MP was three consecutive pulses

Table 1 Clinical and ophthalmological features of 124 patients with Behçet's disease undergoing biologic therapy

Number of patients	124
Age, mean (s.d.), years	38.6 (10.4)
Sex, men/women, *n*/*n*	68/56
HLA-B51 positive, %	66.1
Affected eyes, *n*	221
Pattern of uveitis, *n*	
Bilateral/unilateral	97/27
Anterior	13
Posterior	34
Middle	1
Panuveitis	76
Previous treatment, *n*	
CsA	102
AZA	66
MTX	62
Bolus of i.v. MP	34
First biologic drug used, *n*	
IFX	77
ADA	47
Monotherapy/combined treatment	25/99
Second biologic drug used, *n*	9

ADA: adalimumab; CsA: ciclosporin A; IFX: infliximab; MP: methylprednisolone.

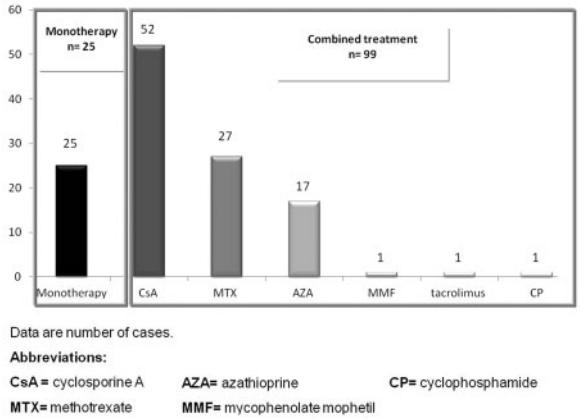
of 500 mg/day (23 cases), six pulses of 500 mg/day (4 cases), three pulses of 1000 mg/day (5 cases) and two pulses of 500 mg/day (2 cases). CsA was used in 102 patients and the mean dose in these patients was 4.8 mg/kg/day (s.d. 0.8). MTX was given to 62 patients [mean dose 16.3 mg/week (s.d. 4.4)] and AZA to 66 patients [mean dose 138.9 mg/day (s.d. 27.9)].

The median period of time from diagnosis of BD until the onset of biologic therapy was 36 months (IQR 16–68).

Biologic therapy

Anti-TNF-α drugs were the first-choice biologic therapy in all 124 patients: IFX in 77 patients (62%) and ADA in the remaining 47 patients (38%) (Table 1). They were used as monotherapy in 25 patients and in combination with conventional immunosuppressive drugs in the remaining 99 patients (Fig. 1). The standard loading dose of IFX (3–5 mg/kg i.v.) was given at 0, 2 and 6 weeks and then the patients received a maintenance dose every 4–8 weeks. The IFX regimen was as follows: (i) 3 mg/kg i.v. and maintenance dose every 4 weeks (1 case), every 6 weeks (1 case) or every 8 weeks (5 cases); (ii) 4 mg/kg i.v. and maintenance dose every 4 weeks (1 case); or (iii) 5 mg/kg i.v. and maintenance dose every 4 weeks (15 cases), every 6 weeks (16 cases), every 7 weeks (1 case) or every 8 weeks (37 cases). The ADA regimen was as follows: (i) 20 mg s.c. every other week (1 case), (ii) 40 mg s.c. every week (1 case) or (iii) 40 mg s.c. every other week (45 cases).

Fig. 1 Biologic treatment as monotherapy or in combination with conventional synthetic immunosuppressive drugs



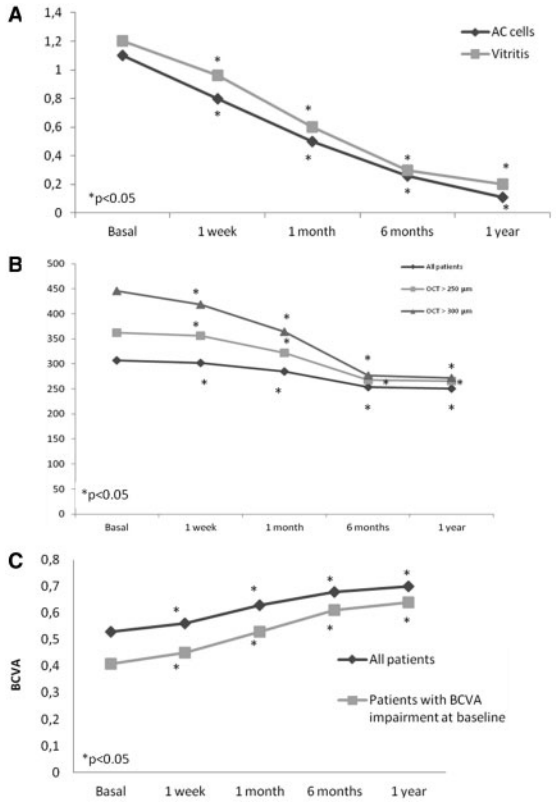
After the first choice of biologic therapy, IFX was switched to ADA in five cases (four because of treatment failure and one due to toxicity) or to rituximab (RTX) in one case (because of toxicity). ADA was switched to IFX in three cases, all because of treatment failure. All the patients were included in the study at the time when the first biologic (anti-TNF-α) agent was used.

Clinical efficacy of anti-TNF-α drugs

Intraocular inflammation, macular thickness, visual acuity, the sparing effect of corticosteroids and immunosuppression load were the outcome variables. All of these showed a rapid and maintained improvement (Figs. 2–4).

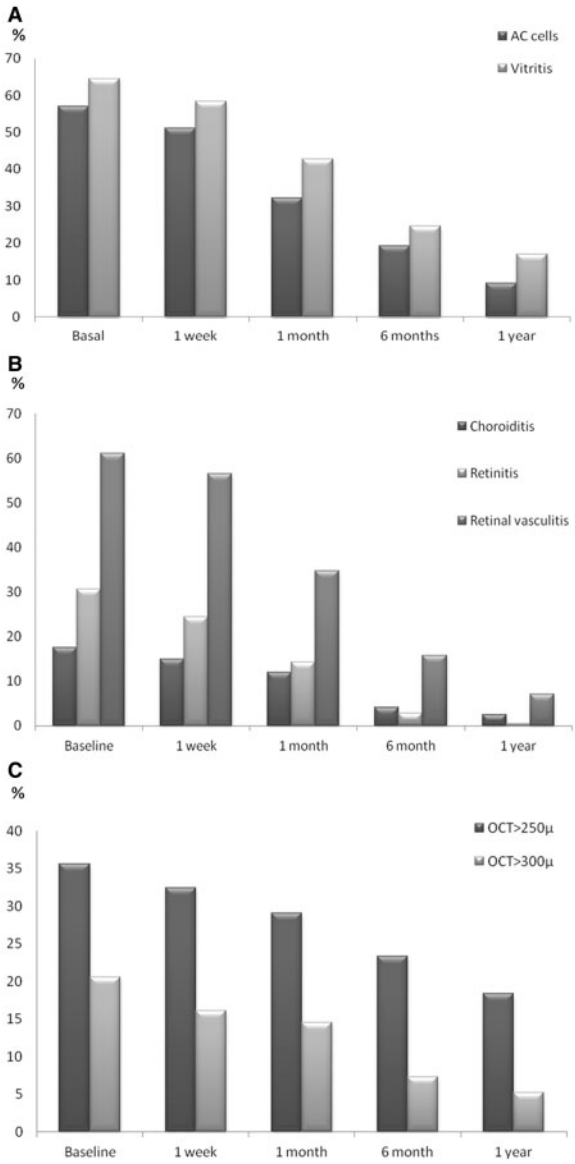
The number of anterior chamber cells, vitritis, macular thickness and BCVA showed a statistically significant improvement that was clinically evident since the first week (Figs. 2A–C). The mean BCVA increased from a median value of 0.3 (IQR −0.1–1) before the onset of biologic therapy to 0.8 (IQR 0.01–1) ($P < 0.01$). A significant reduction in anterior chamber cells [from a median of 1 (IQR 0–2) before the onset of biologic therapy to 0 (IQR 0–0) at 1 year ($P < 0.01$)] and vitritis [from a median of 1 (IQR 0–2) at the onset of biologic therapy to 0 (IQR 0–0) at 1 year ($P < 0.01$)] was also achieved. At the same time, most patients had progressive improvement in intraocular inflammation (Figs. 3A–C). In addition, after 1 year of biologic therapy the number of patients with active choroiditis decreased from 28 (41 eyes) at the onset of biologic therapy to 2 (4 eyes) ($P < 0.01$). Active retinitis that was present in 45 patients (70 eyes) at the onset of biologic therapy was not clinically evident in any patient after 1 year of treatment ($P < 0.01$). Moreover, the number of patients with retinal vasculitis decreased from 89 (143 eyes) to 8 (13 eyes) ($P < 0.01$). At the onset of biologic therapy, 50 patients (80 eyes) had macular thickening (OCT > 250 μm) and 35 patients (49 eyes) had CME (OCT > 300 μm). In these 35 patients, CMO decreased from 420 μm (s.d. 119.5) to 271 (s.d. 45.6) at 1 year ($P < 0.01$).

Fig. 2 Rapid and maintained improvement following the onset of biologic therapy



(**A**) Anterior chamber cells (AC cells) and vitritis, (**B**) macular thickness and (**C**) best corrected visual acuity (BCVA). *$P < 0.05$. Data expressed as mean values compared with basal results. OCT: optical coherence tomography.

Fig. 3 Biologic therapy led to improvement of active inflammation of the different chambers of the eye



Biologic therapy led to improvement of active inflammation of **(A)** anterior chamber cells (AC cells) and vitritis, (**B**) choroiditis, retinitis and retinal vasculitis and (**C**) OCT values. Whenever any score of activity is present, data are expressed as percentage of affected eyes. Active inflammation was considered if AC cells > 0, vitritis > 0, choroiditis or retinitis/retinal vasculitis activity was present and OCT $>250\,\mu$m. OCT: optical coherence tomography.

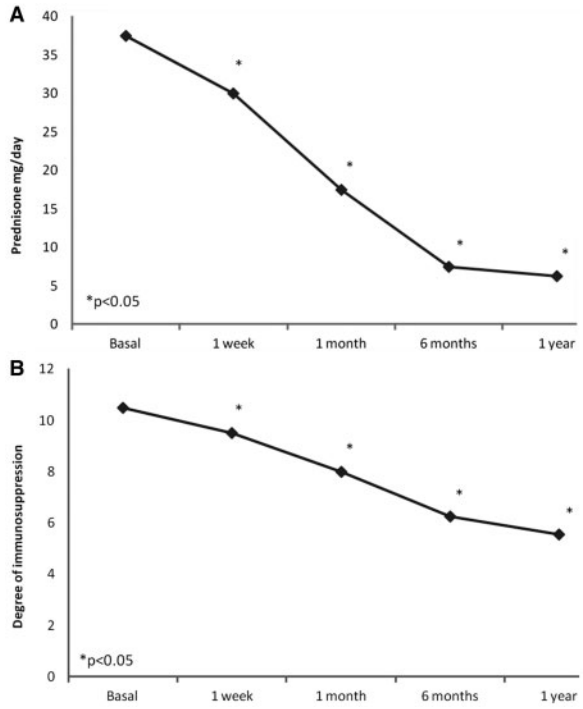
The sparing effect on corticosteroid dose and immunosuppression load score reduction was also observed at 1 year (Fig. 4A and B). With respect to this, the daily median dose of prednisone (or equivalent dose) was reduced from 37.5 mg (IQR 30–60) at baseline to 6.2 mg (IQR 5–10) at 1 year ($P < 0.01$). In addition to this corticosteroid-sparing effect, a reduction in the number of patients that received synthetic immunosuppressive drugs was also achieved. At the end of the survey only 67 of 99 patients were still receiving synthetic immunosuppressive drugs (33 MTX, 15 AZA, 17 CsA and 2 MMF).

Follow-up and side effects

After 1 year of follow-up, complete ocular clinical control of inflammation was achieved in 84 of the 124 patients (67.7%). Because of clinical improvement, the biologic therapy was discontinued in six IFX-treated patients. One of them remained on treatment with CsA and three with MTX. Regrettably, three of these six patients experienced a reactivation of the uveitis. These three patients were on treatment with MTX at the time of recurrence (two received 7.5 mg/week and the other received 12.5 mg/week). In all three cases, inactivity of the uveitis was again achieved after three i.v. doses of IFX therapy.

Biologic therapy was well tolerated in most patients during the 12 months of follow-up. Minor side effects such as mild infusion reactions to IFX and local reactions

Fig. 4 Sparing effect following biologic therapy on corticosteroid dosage and immunosuppression load score



Sparing effect following biologic therapy on (**A**) corticosteroid dosage (values expressed as median of prednisone/day) and (**B**) immunosuppression load score (values expressed as the mean of the score). $^*P < 0.05$.

at the site of ADA injection (pain and erythema) were the most commonly reported complications. However, none of the patients who suffered these minor side effects required discontinuation of the biologic therapy. Two patients who were treated with IFX had severe infusion reactions and were changed to ADA in one case and RTX in the other. Two patients had pneumonia at 4 and 10 months after initiation of ADA. A patient treated with ADA suffered thoracic herpes zoster with good response to antiviral therapy.

Severe complications leading to discontinuation of the biologic therapy were observed in three cases; a patient who had been treated with IFX for 1 month had miliary TB, another patient was diagnosed as having non-Hodgkin's lymphoma after 6 months of ADA therapy and one patient, who died, was diagnosed as having melanoma 3 months after the onset of ADA therapy.

Discussion

Uveitis of BD is a potentially ominous complication that may lead to loss of vision due to irreversible ocular structural damage. The percentage of patients with vision impairment as a result of uveitis due to BD varies depending on the series, but it remains unacceptably high despite conventional systemic immunosuppressive therapy [1, 5, 12–14].

In the last 10 years, biologic immunosuppressive drugs have been used in patients with different inflammatory diseases, including cases with refractory or severe uveitis. Several studies have confirmed the efficacy of these drugs, especially IFX and ADA, in the treatment of uveitis associated with BD. A Japanese study found improvement of uveoretinitis after 1 year of IFX therapy in 44 of 48 patients [39]. However, information is still scarce and generally based on small series or case reports [21, 29, 31–33].

To further investigate this issue, we assessed a series of 124 patients on biologic therapy because of refractory uveitis due to BD. Before the onset of biologic therapy, in an attempt to control ocular inflammation, all the patients received combined therapy that included high-dose corticosteroids and one or more conventional synthetic immunosuppressive drugs. However, despite this procedure, active uveitis persisted. The use of anti-TNF-α therapy in these patients was effective in controlling ocular inflammation. Consequently, anti-TNF-α therapy significantly improved the visual parameters assessed in this study, including macular oedema.

TNF-α is a potent and ubiquitous pro-inflammatory cytokine. IFX is a human/mouse chimeric monoclonal IgG1 antibody specific for TNF-α that is administered intravenously. ADA is a human monoclonal IgG1 antibody also specific for TNF-α that administered subcutaneously.

Unlike in other inflammatory diseases, such as RA, where the initial IFX dose is 3 mg/kg i.v., in most patients with refractory uveitis higher doses (generally 5 mg/kg i.v.) are required to achieve rapid control of intraocular inflammation and avoid loss of vision or blindness. Therefore, in keeping with earlier studies on IFX-treated patients with uveitis [21, 40, 41], most patients with BD uveitis from our series started with 5 mg/kg i.v. at 0, 2 and 6 weeks and then continued with a maintenance dose every 8 weeks. ADA was given subcutaneously, generally at a dosage of 40 mg every other week. Dose adjustment, usually shortening the interval of administration, was required in patients with persistent active or recurrent uveitis.

During follow-up, several patients from our series were switched to a second biologic agent. This was due to insufficient response, because of either lack or loss of efficacy or adverse events. Most of these patients were successfully switched from IFX to ADA or from ADA to IFX. Our experience is in line with previous studies that have suggested that failure of one anti-TNF-α drug does not predict a poor response to a second anti-TNF-α drug [19, 29].

Some reports indicate the potential efficacy of RTX in BD uveitis refractory to treatment with cytotoxic or anti-TNF-α drugs [42–45]. However, in our series we only had data on a single patient who experienced visual improvement following treatment with this drug.

In keeping with earlier reports [18, 29], in our series treatment with anti-TNF-α drugs yielded a corticosteroid-sparing effect, achieving a significant decrease in the median prednisone dose from 37.5 mg/day at the initiation of biologic therapy to 6.2 mg/day after 12 months of biologic therapy.

Some authors have proposed discontinuation of biologic therapy in patients with persistent inactive ocular inflammation [18, 29]. Since biologic therapy is not free of adverse effects, and the cost is relatively high, we tried to discontinue the biologic drug in six patients with sustained clinical inactivity. Regrettably, as observed in other studies, three of the patients experienced reactivation of the uveitis [24, 46]. Therefore, because of the high risk of relapse, we suggest performing close follow-up of patients who discontinue biologic therapy.

In our experience, the number of patients suffering any adverse effects following anti-TNF-α therapy throughout the first year of follow-up was lower than in other series [21]. The most common side effects were mild infusion reactions with IFX and skin reactions at the injection site with ADA.

A major concern is the propensity of patients on anti-TNF therapy to develop reactivation of latent TB [47]. Nevertheless, probably due to our concern about this potential complication, TB following anti-TNF-α therapy occurred in only a single case in our series.

It should be noted that two of the patients from this series developed cancer while they were undergoing biologic therapy. The risk of cancer associated with the use of anti-TNF-α is controversial because there are studies showing that TNF-α exerts both pro- and anticancer properties [48]. However, a recent meta-analysis did not demonstrate an increased risk of cancer in patients with RA treated with anti-TNF-α compared with placebo [49].

Because of this, we cannot confirm that the development of cancer in these two cases was the result anti-TNF-α therapy.

IFN-α has proved to be a useful drug in the management of patients with uveitis secondary to BD [50]. However, the use of IFN is often associated with side effects such as fatigue. Because of this, in this multicentre study in which most uveitis units in Spain were included, the use of anti-TNF-α was preferred [51–53]. There are several limitations due to the observational nature of the study. Thus a randomized trial comparing anti-TNF-α agents and IFN-α is needed. In conclusion, the results from our present series support the claim that anti-TNF-α therapy is effective and relatively safe in refractory BD uveitis.

Rheumatology key messages

- Anti-TNF-α therapy is effective and relatively safe in refractory uveitis due to Behçet's disease.
- Anti-TNF-α drugs yielded a corticosteroid-sparing effect in refractory uveitis due to Behçet's disease.

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Clinical vignette

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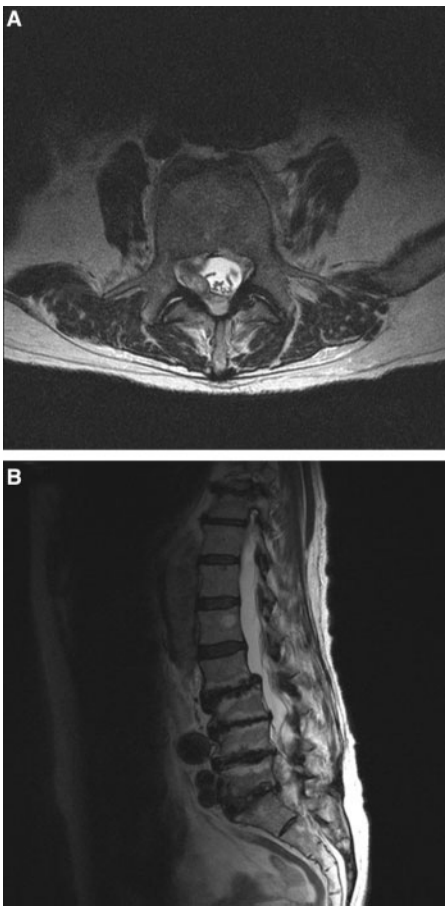
Staphylococcus lugdunensis septic arthritis and epidural abscess in a patient with rheumatoid arthritis receiving anti-tumour necrosis factor therapy

A 74-year-old man with RA, well controlled on etanercept (50 mg/week) and prednisolone (7 mg/day), presented with septic arthritis affecting the right knee. He was afebrile, but hyper-reflexic in both legs with L3–L5 dermatomal sensory loss. Synovial fluid and peripheral blood cultures grew coagulase-negative staphylococci, speciated as *Staphylococcus lugdunensis*. MRI demonstrated an extensive epidural abscess (Fig. 1).

FIG. 1 T2-weighted MRI of the lumbosacral spine



(**A**) Axial and (**B**) sagittal images. Imaging demonstrated an extensive epidural abscess centred at L5, effacement of the thecal sac with compression of the roots of the cauda equina and abnormal signal in the L2–L5 vertebral bodies with dural and intradisc enhancement consistent with discitis and vertebral osteomyelitis.

Intravenous antibiotic therapy with flucloxacillin and sodium fusidate was initiated and etanercept was discontinued. The knee was washed out and the neurosurgical team opted to manage the abscess conservatively. Antibiotics were continued for 16 weeks, with which the neurological and radiological signs resolved and CRP normalized. Two years later the patient remains well with quiescent RA without reinstitution of biologic therapy.

There are single previous reports of *S. lugdunensis* infecting a native joint (in a patient with longstanding RA [1]) and of epidural abscess following haematogenous seeding from cellulitis [2]. Disseminated musculoskeletal infection (including epidural abscess) as observed in this case, in the context of anti-TNF use, is unique. This contributes to the literature on its occurrence in the immunocompromised, in whom signs of sepsis can be masked. Nonetheless, this case demonstrates that, despite high virulence, such patients can be managed successfully with antimicrobial therapy and close monitoring.

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