Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behçet’s disease: multicentre retrospective study

Belén Atienza-Mateo, Vanesa Calvo-Río, Emma Beltrán, Lucía Martínez-Costa, Elia Valls-Pascual, Marisa Hernández-Garfella, Antonio Atanes, Miguel Cordero-Coma, Joan Miquel Nolla, Carmen Carrasco-Cubero, Javier Loricera, Maria C. González-Vela, Nuria Vegas-Revenge, Carlos Fernández-Díaz, Rosalia Demetrio-Pablo, Lucía C. Domínguez-Casas, José Luis Martín-Varillas, Natalia Palmou-Fontana, José L. Hernández, Miguel Á. González-Gay and Ricardo Blanco

Abstract

Objective: To assess the efficacy of tocilizumab (TCZ) in refractory uveitis of Behçet’s disease (BD).

Methods: Multicentre study of patients with BD-associated uveitis. Patients were refractory to conventional and biologic immunosuppressive drugs. The main outcome measures were intraocular inflammation, macular thickness, visual acuity and corticosteroid-sparing effects.

Results: We studied 11 patients (7 men) (20 affected eyes); median age 35 years. Uveitis was bilateral in nine patients. The patterns of ocular involvement were panuveitis (n = 8, with retinal vasculitis in 4), anterior uveitis (n = 2) and posterior uveitis (n = 1). Cystoid macular oedema was present in seven patients. The clinical course was recurrent (n = 7) or chronic (n = 4). Before TCZ, patients had received systemic corticosteroids, conventional immunosuppressants and the following biologic agents: adalimumab (n = 8), infliximab (n = 4), canakinumab (n = 1), golimumab (n = 3), etanercept (n = 1). TCZ was used as monotherapy or combined with conventional immunosuppressants at 8 mg/kg/i.v./4 weeks (n = 10) or 162 mg/s.c./week (n = 1). At TCZ onset the following extraocular manifestations were present: oral and/or genital ulcers (n = 7), arthritis (n = 4), folliculitis/pseudofolliculitis (n = 4), erythema nodosum (n = 2), livedo reticularis (n = 1) and neurological involvement (n = 2). TCZ yielded rapid and maintained improvement in all ocular parameters of the patients, with complete remission in eight of them. However, this was not the case for the extraocular manifestations, since TCZ was only effective in three of them. After a mean (S.D.) follow-up of 9.5 (8.05) months, TCZ was withdrawn in two cases, due to a severe infusion reaction and arthritis impairment, respectively.

Conclusion: TCZ could be a therapeutic option in patients with BD and refractory uveitis.

Key words: Behçet’s disease, uveitis, anti-TNF therapy, tocilizumab
Introduction

Behçet’s disease (BD) is a chronic vasculitis characterized by recurrent oral ulcers and systemic manifestations including ocular, skin, gastrointestinal, neurologic, vascular and joint involvement [1]. Ocular involvement can be found in 35–80% of cases, depending on the reported series [2]. It is a potentially severe and disabling complication that may lead to a significant decrease in visual acuity. The risk of severe visual loss ranges from 13 to 74% within 6–10 years [3, 4]. Posterior segment involvement is the most common cause of blindness, with cystoid macular oedema (CME) being the most important aetiology [5, 6].

The prognosis of ocular involvement has improved over the last decades due to the use of conventional and biological immunosuppressive therapies [7].

According to the ‘Expert panel recommendations for the use of anti-TNF-α drugs in patients with ocular inflammatory disorders’, published in 2014, infliximab (IFX) or adalimumab (ADA) may be used as first- or second-line corticosteroid-sparing therapy in patients with ophthalmic manifestations of BD [8]. In 2016, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [http://www.fda.gov] (http://www.ema.europa.eu) approved ADA for use in non-infectious intermediate, posterior and panuveitis, including those due to BD, based on two randomized double-blinded studies [9, 10].

Anti-TNF-α agents have contributed to the improvement of visual outcome in BD-related uveitis refractory to conventional immunosuppressive drugs [11]. However, ADA and/or IFX do not achieve control of intraocular inflammation in all patients and in some cases these biologic agents are not well tolerated.

IL-6 is a pleiotropic cytokine that has been implicated in the pathogenesis of immune-mediated diseases including non-infectious uveitis. Increased IL-6 concentrations have been demonstrated in the vitreous fluid of chronic or acute uveitis patients [12]. Tocilizumab (TCZ) is a humanized mAb against IL-6 receptor, approved for the treatment of some inflammatory diseases such as RA, systemic JIA and Castleman’s disease [13]. TCZ has also shown efficacy in different refractory ocular inflammatory diseases such as uveitis related to JIA or birdshot choriotretniopathy [14, 15]. However, experience with TCZ in BD-related uveitis is still scarce [16, 17].

Taking into account all these considerations, our aim was to evaluate the response to TCZ in BD-related uveitis refractory to standard systemic treatment. Its efficacy in other extraocular manifestations of the disease was also evaluated.

Methods

Design and enrolment criteria

An observational case series, multicentre, retrospective study was conducted in patients diagnosed with BD-related uveitis with partial or no response to corticosteroids. Patients were required to be refractory to at least one standard synthetic immunosuppressive drug and, in most cases, to another biologic drug, usually an anti-TNF-α agent. Patients were studied at the outpatient clinics of the Uveitis Units of several referral centres.

The diagnosis of BD was performed according to the proposed International Criteria for BD [18]. In addition, all of the patients fulfilled the recent proposed criteria for BD [19]. Malignancy or systemic infectious diseases, including hepatitis B or hepatitis C infection, were excluded before TCZ onset, as previously described [11, 14, 15, 17, 20–22]. To exclude latent tuberculosis, a tuberculin skin testing (Purified Protein Derivative, PPD, AJ Vaccines A/S, Copenhagen S, Denmark) and/or an Interferon-γ (IFN-γ) assay (quantiFERON, TB Gold Plus (QFT-Plus), Qiagen, Hilden, Germany) and a chest radiograph were performed on all patients receiving biologic drugs, as indicated by the Spanish National Guidelines. If present, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic agent and maintained for 9 months.

Uveitis was anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group [23]. Remission was defined as the presence of inactive disease for at least 3 months.

Since TCZ is an off-label indication for uveitis, written informed consent was requested and obtained from all the patients.

Primary or secondary failure to biologic therapy other than TCZ was defined if patients never experienced a good response to biologic agents (primary failure) or they initially had a good response but later the biologic agents lost efficacy (secondary failure).

Patients were treated with TCZ as monotherapy or combined with conventional immunosuppressive drugs. TCZ was used at the standard dose of 8 mg/kg i.v./4 weeks or 162 mg/s.c./week.

Outcome variables

As discussed above, the main outcome measures were intraocular inflammation, macular thickness, visual acuity and corticosteroid-sparing effects. These outcome variables were recorded in all patients at baseline and at 1 week, 1, 3 and 6 months, and 1 year after TCZ onset. They were assessed in each centre according to a follow-up protocol agreed beforehand. Any other extraocular manifestations of BD were also assessed.

The degree of intraocular inflammation was evaluated according to the SUN Working Group [23]. The Nussenblat scale was used to evaluate the degree of vitritis [24].

Following SUN recommendations, improvement of anterior uveitis activity was defined as either a two-step decrease in the level of inflammation or a decrease to reach grade 0 in the level of inflammation (the scale is the following: 4, 3, 2, 1, 0.5 and 0). A worsening activity was defined as either a two-step increase in the level of inflammation or an increase to grade 4 [23]. Inactive anterior uveitis was defined as <1 cell per field in the anterior chamber on slit lamp examination (grade 0). Similar definition was used for improvement of vitritis haze.
Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on fluorescein angiogram. Choroiditis and retinitis were considered active or inactive depending on the presence or absence of activity data on the ophthalmic examination and/or in the fluorescein angiogram.

Macular thickness was measured by high-definition optical coherence tomography (HD-OCT). All HD-OCT scans were performed using 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 μm, and CME was considered to be present when it was >300 μm. Visual acuity was expressed as the best-corrected visual acuity.

Statistical analysis
Statistical analysis was performed using the software STATISTICA (StatSoft Inc., Tulsa, OK, USA). Results were expressed as mean (± SD) for variables with a normal distribution, or as median [interquartile range (IQR)] when they were not normally distributed. The comparison of continuous variables among time periods was performed using the Wilcoxon signed rank test.

Results
Baseline data at TCZ onset
Eleven patients (7 men/4 women; 20 affected eyes) with uveitis refractory to conventional immunosuppressive therapy (n = 11) and at least one anti-TNF-α drug (n = 10) were studied. The median age (IQR) was 35 (22–50) years.

Uveitis was bilateral in nine patients. The patterns of ocular involvement were panuveitis (n = 8), with retinal vasculitis in four cases, anterior uveitis (n = 2) and posterior uveitis (n = 1). CME was present in seven patients. The clinical course was chronic (four patients) or recurrent (seven patients). The main baseline features of our sample are shown in Table 1.

Besides oral corticosteroids and before the onset of the first biologic agent, patients had been treated with intraocular corticosteroids (n = 10), pulses of intravenous methylprednisolone (n = 10), MTX (n = 9), CsA (n = 8), AZA (n = 3), CYC (n = 2) and MMF (n = 1).

Previous biologic agents before TCZ
Before TCZ therapy, 10 of the 11 patients had also received biologic agents (Fig. 1): ADA (n = 7), IFX (n = 2), canakinumab (n = 1) or daclizumab (n = 1). Several conventional immunosuppressive drugs had been administered in combination with these biologic agents: MTX (n = 6), CsA (n = 1) and AZA (n = 1). Treatment with these biologic agents had to be withdrawn because of a primary (six cases) or a secondary failure (two cases), or adverse events (two cases).

Therapy with TCZ
TCZ was started in all cases because of refractory uveitis (Table 1). Cataracts, as ocular sequelae, were found in three cases at TCZ onset. TCZ was used at the standard intravenous dose (8 mg/kg/i.v./4 weeks) in 10 patients or subcutaneously (162 mg/s.c./week) in one case. TCZ was administered as monotherapy in seven cases and combined with conventional immunosuppressive drugs in the remaining four cases (MTX in two, and CsA and AZA in one patient each). At the onset of TCZ therapy all patients were taking oral glucocorticoids. Following TCZ therapy all patients were able to reduce the glucocorticoid dose progressively, leading to complete discontinuation in eight of them. In the remaining three patients, the median dose of prednisone (or equivalent) at last visit was only 5 mg/day. Before the onset of TCZ nine patients had required intraocular injections of glucocorticoids. However, only one patient required a single injection of intraocular glucocorticoids after the onset of TCZ therapy. As shown in Fig. 2, the outcome variables showed a rapid and maintained improvement following TCZ therapy.

After a mean (± SD) follow-up of 9.5 (8.05) months, all patients experienced an improvement of the best-corrected visual acuity [mean 0.38 (0.32–0.73) (0.35); P = 0.002]. Fig. 2 shows the improvement in anterior chamber cells and vitritis. After 3 months of therapy all the patients in whom this information was available showed an improvement of anterior chamber cells according to SUN criteria. Such an improvement was maintained at 6 months and after 1 year of treatment (Fig. 2). At baseline, 10 of 11 (90.9%) patients had active vitritis. At month 12, all patients had a grade 0 score in the Nussenblat scale.

The median (IQR) OCT decreased from 356 (260–398) to 241.5 (235–243) μm (P = 0.01). Complete resolution of retinal vasculitis (n = 8 eyes), choroiditis (n = 3 eyes) and retinitis (n = 3 eyes) observed at the onset of TCZ therapy was achieved in all affected patients at last follow-up. Also, CME (nine eyes at the onset of TCZ therapy) only persisted in one eye at the end of follow-up. Furthermore, prednisone dose was reduced [from a median dose of TCZ onset of 30 (IQR: 20–30) to 0 (0–5) mg; P = 0.005]. Overall, eight patients obtained a complete ocular remission. None of patients included in this study had ocular hypertension at the beginning of TCZ therapy or during the follow-up.

The following extraocular manifestations were also present at the onset of TCZ therapy: oral and/or genital ulcers (n = 7), only oral involvement in two of them), arthritis (n = 4), folliculitis/pseudofolliculitis (n = 4), erythema nodosum (n = 2), livedo reticularis (n = 1) and neurological involvement (one patient with papillitis and one patient with haemorrhagic stroke). Overall, TCZ therapy did not yield clinical improvement of most of the extraocular manifestations. It was effective in only four with extraocular manifestations. Mucous ulcers only improved in one of the seven patients and arthritis in only two of the four patients. This was also the case for erythema nodosum in the setting of BD, which only improved in one of two patients.

TCZ had to be withdrawn in two patients due to complications unrelated to the uveitis; in one of them because of a severe infusion reaction, and in the other due to impairment of arthritis. The follow-up after TCZ discontinuation in these
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (years)</th>
<th>HLA B51</th>
<th>Conventional/biological immunosuppressive drugs before TCZ</th>
<th>Conventional immunosuppressive drug associated with TCZ</th>
<th>Ocular pattern/course</th>
<th>Extraocular manifestations</th>
<th>Manifestations that improved with TCZ therapy</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male/27</td>
<td>Positive</td>
<td>MTX, CsA, CFM/ADA, GLM</td>
<td>MTX</td>
<td>Bilateral posterior uveitis + unilateral CME/chronic</td>
<td>Oral ulcers, asymptomatic white matter lesions on MRI, arthritis, folliculitis</td>
<td>Uveitis and CME</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Female/42</td>
<td>Positive</td>
<td>MTX, CsA, AZA, CFM/ADA, GLM</td>
<td>--</td>
<td>Bilateral panuveitis + unilateral CME/chronic</td>
<td>Oral and genital ulcers, erythema nodosum</td>
<td>Uveitis and CME</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Male/50</td>
<td>Positive</td>
<td>MTX, CsA/ADA, GLM</td>
<td>--</td>
<td>Panuveitis and papillitis bilateral + unilateral CME/relapsing</td>
<td>Papillitis, arthritis</td>
<td>All (uveitis, papillitis, CME and arthritis)</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Male/35</td>
<td>Positive</td>
<td>MTX, CsA, AZA, MMF/daclizumab, IFX</td>
<td>--</td>
<td>Bilateral panuveitis + retinal vasculitis/relapsing</td>
<td>Oral ulcers, folliculitis</td>
<td>Uveitis and retinal vasculitis</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>Female/67</td>
<td>Positive</td>
<td>MTX, CsA/ADA, IFX</td>
<td>--</td>
<td>Bilateral panuveitis + retinal vasculitis + bilateral CME/relapsing</td>
<td>Livedo reticularis</td>
<td>Uveitis, retinal vasculitis and CME</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Male/31</td>
<td>Negative</td>
<td>MTX, CsA/ADA, IFX</td>
<td>--</td>
<td>Unilateral panuveitis + retinal vasculitis + unilateral CME/relapsing</td>
<td>Oral and genital ulcers, folliculitis</td>
<td>Uveitis, retinal vasculitis and CME</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Female/22</td>
<td>Positive</td>
<td>MTX, CsA/ADA, CsA</td>
<td>CsA</td>
<td>Bilateral panuveitis + bilateral CME/chronic</td>
<td>None</td>
<td>Uveitis and CME</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Male/75</td>
<td>Positive</td>
<td>MTX, CsA/ADA, IFX</td>
<td>--</td>
<td>Bilateral panuveitis + retinal vasculitis + unilateral CME/relapsing</td>
<td>Oral and genital ulcers, arthritis, folliculitis</td>
<td>Uveitis, retinal vasculitis and arthritis</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>Male/10</td>
<td>Positive</td>
<td>--/Canakinumab, IFX</td>
<td>--</td>
<td>Bilateral anterior uveitis/relapsing</td>
<td>Oral and genital ulcers, haemorrhagic stroke, erythema nodosum</td>
<td>Uveitis, oral and genital ulcers and erythema nodosum</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>Female/48</td>
<td>Positive</td>
<td>MTX, colchicine/IFX, ADA, GLM</td>
<td>MTX</td>
<td>Bilateral anterior uveitis/relapsing</td>
<td>Oral and genital ulcers, arthritis, pseudofolliculitis, erythema nodosum, intestinal involvement</td>
<td>Uveitis</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td>Male/16</td>
<td>Positive</td>
<td>AZA/ADA, IFX</td>
<td>AZA</td>
<td>Unilateral panuveitis/chronic</td>
<td>Oral ulcers, arthritis</td>
<td>Uveitis</td>
<td>4</td>
</tr>
</tbody>
</table>

---

none; ADA: adalimumab; CFM: cyclophosphamide; ETN: etanercept; GLM: golimumab; IFX: infliximab; TCZ: tocilizumab; CME: cystoid macular oedema.
Fig. 1 Flow-chart of 11 patients with refractory Behçet’s disease-related uveitis receiving tocilizumab therapy

ADA: adalimumab; CANA: canakinumab; ETN: etanercept; GLM: golimumab; IFX: infliximab; TCZ: tocilizumab.

Fig. 2 Rapid and maintained ocular improvement following tocilizumab therapy

(A and B) Percentage of improvement on anterior chamber (AC) cells and vitritis according to the Standardization of Uveitis Nomenclature (SUN) Working Group criteria following tocilizumab therapy. (C) Improvement in the best corrected visual acuity (BCVA). (D) High-definition optical coherence tomography (HD-OCT) showing improvement following treatment with tocilizumab.
sive drugs and most of them to anti-TNF-related uveitis refractory to conventional immunosuppressants. This is the reason why we conducted this study.

For patients who do not improve or who are intolerant to these biologic agents, who still some BD patients with uveitis who [14, 25] drugs in the treatment of non-infectious refractory uveitis neutropaenia, thrombocytopaenia and gastrointestinal infection, increased transaminases level, hyperlipidaemia, agents. With TCZ reported in the literature include upper respiratory tract therapy, as demonstrated in RA. The main side effects of IFX for acute panuveitis attacks in BD has also been mediated by IFX anti-TNF agents, who could suffer relapses of uveitis in the future.

Unlike anti-TNF antibodies, TCZ can be used as monotherapy, as demonstrated in RA. The main side effects of TCZ are not fully understood. Nevertheless, it is known that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. We recently showed that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. Furthermore, IL-6 has a wide range of pleiotropic effects, including induction of acute-phase reactant production by hepatocytes, B-lymphocyte differentiation and T-lymphocyte subset differentiation. TCZ is a humanized mAb against soluble and membrane-bound IL-6 receptor that has been approved for the treatment of autoimmune and inflammatory diseases, such as RA, systemic vasculitis syndromes, including vasculitis syndromes [33, 34]. TCZ has also shown efficacy in other systemic and polyarticular juvenile arthritis, and Castleman’s disease [28]. TCZ has also shown efficacy in other systemic diseases, including vasculitis syndromes [29, 30, 32].

The mechanisms by which TCZ leads to a clinical improvement are not fully understood. Nevertheless, it is known that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. Moreover, TCZ has demonstrated efficacy in patients with classical rheumatoid arthritis, as demonstrated in RA. The main side effects of TCZ, including the data shown in the present study, are not fully understood. Nevertheless, it is known that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. Overall, TCZ yielded a rapid reduction of ocular inflammation in these patients. Also, the data shown in Fig. 2 help to appreciate the rapidity of onset of TCZ. On the other hand, the use of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis. The mechanisms by which TCZ leads to a clinical improvement are not fully understood. Nevertheless, it is known that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. Moreover, TCZ has demonstrated efficacy in patients with classical rheumatoid arthritis, as demonstrated in RA. The main side effects of TCZ, including the data shown in the present study, are not fully understood. Nevertheless, it is known that IL-6 blockade may suppress autoantibody production and/or Th17 vs Th17. Overall, TCZ yielded a rapid reduction of ocular inflammation in these patients. Also, the data shown in Fig. 2 help to appreciate the rapidity of onset of TCZ. On the other hand, the use of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Discussion

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveits.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis. This is the reason why we conducted this study.

Several studies have confirmed the efficacy of anti-TNF agents, who could suffer relapses of uveitis in the future. Our results indicate that TCZ may be effective in highly refractory BD-related uveitis.
perforation [37]. Nevertheless, in our study, the only severe adverse effect found was an infusion reaction.

Two interventional randomized multicentre phase II trials focusing on IL-6 as the target for non-infectious uveitis treatment are ongoing [12]. They are the STOP-UVEITIS Study, aiming to analyse the safety, tolerability and bioactivity of TCZ on patients with non-infectious uveitis, and the SATURN Study, designed to evaluate the efficacy of sarilumab (another anti-IL-6 receptor mAb) in non-infectious uveitis.

Besides TCZ, IL-1 blocking agents have also shown promising results in mucocutaneous, eye and neurologic involvement of BD [38, 39]. BD patients with an initial low response to anakinra, a recombinant human IL-1 receptor antagonist, have shown complete resolution of symptoms [40] by increasing the dose of this biologic agent [40]. Switching to canakimumab, a human immunoglobulin G1 anti-IL-1β mAb, after a failure of a first anti-IL-1 agent, has also been proposed in refractory patients [41].

The response to the different biologic agents in patients with BD depends on the type of clinical manifestation (Table 3). Mucocutaneous lesions can be controlled with IFN-α therapy, and several studies have confirmed significant decrease in aphthous ulceration and papulopustular lesions with this agent. Anti-TNF mAb may be effective in BD with ocular, vascular, neurologic and gastrointestinal involvement refractory to conventional immunosuppressive agents [42]. However, TCZ in BD patients with extracutaneous manifestations has shown contradictory results. In this regard, TCZ was reported to be useful in genital ulcers [35, 43] and refractory neuro-Behcet’s [44–46]. In contrast, TCZ does not yield improvement and in some cases may even worsen skin and mucosal manifestations [47, 48]. In our series, the overall response of TCZ for extracutaneous manifestations was poor. As a result, the therapeutic approach for BD should be individualized depending on the prevailing clinical manifestation.

In conclusion, our study yields promising results on the efficacy of TCZ in the management of BD patients with refractory uveitis. According to our data, TCZ could be a therapeutic option in patients with BD and refractory uveitis.

Disclosure statement: R.B. has received grants and/or research supports from Abbott, Merck Sharp & Dohme (MSD) and Roche, and had consultation fees and/or participation in company sponsored speaker’s bureau from Abbott, Pfizer, Roche, Bristol-Myers, Janssen and MSD. M.A.G.-G. received grants/research supports from Abbott, MSD and Roche, and had consultation fees and/or participation in company-sponsored speaker’s bureau from Abbott, Pfizer, Roche, Jansen, Sanofi and MSD. M.C.-C. has received speaker fees and research and/or grant support from Union chimique belge, Allergan and AbbVie. All other authors have declared no conflicts of interest.

Table 3: Biologic therapy efficacy in the main clinical manifestations of Behcet’s disease

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>IFN-α</th>
<th>Anti-TNF mAb</th>
<th>ETN</th>
<th>Anakinra</th>
<th>TCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous (oral and genital ulcers)</td>
<td>++</td>
<td>++</td>
<td>+ (oral)</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Ocular</td>
<td>±</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Neurological</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Vascular</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Articular</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

++: clear improvement; +: improvement; ±: contradictory data; −: impairment; ETN: etanercept; TCZ: tocilizumab.

References


Clinical Vignette

Ochronosis: a close mimic of ankylosing spondylitis

A 50-year-old woman presented to us with chronic low back ache for 10 years with gradually progressive kyphosis. The backache was mechanical in nature with early morning stiffness of less than 15 minutes. She had partial response to NSAIDs and other analgesics (tramadol and paracetamol). Physical examination revealed brown pigmentation of the sclera and ear pinna bilaterally (Fig. 1A and 1B). On inquiry, she reported that her urine had turned dark on exposure to air since childhood. A radiograph showed narrowing of intervertebral spaces and intervertebral disc calcification of the thoracic and lumbar spine with normal sacroiliac joints (Fig. 1C and 1D). Based on these findings, a diagnosis of ochronosis was reached. Measurement of 24 h urinary homogentisic acid levels was offered but declined due to financial constraints. She was born to non-consanguineous parents. No other family members were affected with similar complaints. The patient was started on ascorbic acid, an antioxidant that reduces the production of oxidized homogentisic acid.

Ochronosis is a rare autosomal recessive disorder of tyrosine metabolism where deficiency of the enzyme homogentisate 1,2-dioxygenase leads to accumulation of oxidized homogentisic acid in the connective tissues, causing ochre-like pigmentation of the skin, sclera and cartilage. Ochronotic arthropathy affecting the spine generally appears in the third decade. Narrowing of the intervertebral spaces and wafer-like disc calcification are diagnostic findings seen on spine radiographs, as is in this case [1]. The disease may be misdiagnosed as AS, which is a close mimic [2].

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Suvrat Arya1, Vikas Gupta1 and Vikas Agarwal1

1Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Correspondence to: Vikas Gupta, Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Rae Bareli Road, Lucknow, Uttar Pradesh 226014, India. E-mail: vikasagcapri@yahoo.co.in

References


Fig. 1 Clinical and radiographic features of ochronosis in our patient

Photographs show greyish-blue pigmentation of the ear pinna (panel A, arrows) and blue-black pigmentation of the sclera (panel B, arrow). Spinal radiographs show narrowing of the intervertebral spaces and intervertebral disc calcification (panels C and D, arrows) with sparing of the sacroiliac joints.