Long-term efficacy of infliximab in refractory posterior uveitis of Behc¸et’s disease: a 24-month follow-up study


Objectives. To evaluate the long-term efficacy and safety of infliximab in patients with Behc¸et’s disease (BD) and refractory bilateral posterior uveitis, and to assess the proportion of relapse-free subjects through months 12 and 24.

Methods. Open-label, multicentre, 24-month, prospective, follow up study on 12 consecutive patients with BD and refractory posterior uveitis who had failed at least one immunosuppressive drug. At baseline patients received prednisolone 1 mg/Kg/day with rapid tapering and nine infliximab infusions (5 mg/kg) over a 12-month period. Non-responders after the third infusion withdrew from the study. Patients were evaluated for ocular inflammation degree, visual acuity (VA), number of ocular attacks and incidence of adverse events (AEs).

Results. At 12-month visit, 9/12 (75%) patients achieved a complete remission with no relapse during the treatment period. All had a dramatic improvement of ocular inflammation after the first infusion, six were in complete remission after three infusions, and three after four. All these patients suspended corticosteroids at week 22. At 24-month visit, seven out of nine (78%) were still in remission. Mean VA improved from 0.2 ± 0.6 to 0.5 ± 0.2 (P < 0.001), and ocular attacks dropped from 40 in the year before therapy to 5 after infliximab cessation (P < 0.001). One patient had a partial remission with two relapses during treatment, and 2/12 (17%) patients showed no improvement. Infliximab was well tolerated with no serious AEs.

Conclusions. Infliximab is rapidly effective and safe in a high proportion BD patients with refractory posterior uveitis, and may be helpful to prevent recurrences.

Key words: Infliximab, Anti-TNF-α drugs, Behc¸et’s disease, Uveitis, Retinal vasculitis.

Introduction

Uveitis of Behc¸et’s disease (BD) may be particularly resistant to corticosteroids and immunosuppressants with rapid progression to vision loss in 10–25% of the cases [1–3]. Therapeutic strategies are based on few controlled trials on small clinical series, and evidence is based currently on open, short-term studies, while the long-term ones are usually retrospective. Therapy is usually administered until ocular manifestations subside, and successively tapered and interrupted after months or years on the basis of single clinician’s judgement [4, 5].

In animal models TNF-α plays a key role in the pathogenesis of ocular inflammation [6–8], and serum and intraocular increased concentrations of TNF-α have been detected in patients with active BD [9, 10].

Due to this evidence, some BD patients with refractory posterior uveitis have been treated with at least four infusions of infliximab, a chimeric monoclonal anti-TNF-α antibody [10–13]. All patients experienced a rapid remission of ocular inflammation over a few days.

Primary end point of this open label, multicentre, 24-month follow up, prospective study was to describe the long-term efficacy and safety of 12-month infliximab infusions in 12 consecutive patients with BD and refractory bilateral posterior uveitis.

Patients and methods

Primary end point

To assess the efficacy and safety of infliximab in patients with BD and refractory posterior uveitis as expressed by the percentage of patients achieving a complete or partial remission.

Secondary end-points

To evaluate the incidence of adverse events (AEs), the efficacy of infliximab to reduce or prevent ocular attacks as expressed by the frequency of ocular attacks during the 12-month treatment period compared with the 12-month period before infliximab therapy, visual acuity (VA) improvement; the proportion of relapse-free subjects through months 12 and 24.

All consecutive patients meeting the ISG criteria for the diagnosis of BD [14] followed up in three Italian Rheumatology Centers (Prato, Firenze and Reggio Emilia), who had refractory bilateral posterior uveitis were recruited over a 12-month period. All patients had chronic, bilateral sight-threatening uveitis, with or without retinal vasculitis, resistant to treatment to high dose corticosteroids associated to at least one immunosuppressive drug [15, 16].

Refractory posterior uveitis was diagnosed by an ophthalmologist by a complete ocular examination including best-corrected VA (Snellen chart of 0.1–1.0 at a distance of 5 m), slit-lamp biomicroscopy, tonometry and ophthalmoscopy, and fundus fluorescein angiography (FAG). In addition, patients were clinically assessed by a rheumatologist for any concurrent manifestation of BD.

Treatment regimen

At baseline, all patients suspended the current immunosuppressive therapy, and received prednisone at the dose of 1 mg/kg/day.
In addition, all subjects received infliximab 2-h intravenous infusions at the dose of 5 mg/kg at weeks 0, 2, 6, 14, 22, 30, 38, 46 and 54.

In responders, the following corticosteroid dose tapering was scheduled: 10 mg/day every 1 week until the dose of 20 mg/day, then 5 mg/day/week until a maintenance dose of 10 mg/day. This dose was continued for at least 2 weeks before attempting to further reduce the dose of 5 mg/week until withdrawal.

In case of relapse, prednisone was increased by 20 mg/day. Other immunosuppressant agents, and concomitant local corticosteroids injections were not allowed.

Patients failing to achieve at least a partial remission after the third infusion of infliximab withdrew from the study and received prednisolone 1 mg/kg/day and an immunosuppressant different from that employed before the study entry.

Exclusion criteria

A negative pregnancy test was required for non-menopausal female patients and contraception was recommended to all females of childbearing potential.

Patients with a history of recent infections and neoplasms were excluded from the study. Moreover, a careful screening for tuberculosis was made by detailed medical history, chest X-rays and PPD test.

During the drug infusion and for 1 h afterwards, blood pressure, pulse and temperature were measured every 30 min. Moreover, at every visit, complete blood count, liver and kidney function tests were examined. Antinuclear antibodies (ANA) were measured at baseline, weeks 30 and 54.

Patients were evaluated at baseline and the day after the infusion for the following outcome measures:

**Complete remission.** Presence of less than 1+ cellular reaction (scale 0–4), and remission of vasculitis evaluated by a score from 0 to 3 at fundus examination and FAG (0 = absence of vasculitis, 1 = vasculitis of peripheral retinal vessels, 2 = posterior pole vasculitis, 3 = vasculitis with evidence of areas of retinal necrosis). FAG examinations were scheduled at baseline, week 6, 22, and 54, and at month 24.

**Partial remission.** Improvement of at least 50% of inflammation and retinal vasculitis scores.

**Non-responder.** Absence of any improvement or <50% of uveitis scores.

At each visit best corrected VA was measured.

The follow-up period was 24 months. Over the 12 month, off-therapy period, the follow-up visits were scheduled every 2 months or less in the case of relapse.

Study approval by the local ethical committee and patient written informed consent were obtained.

Data statistical analysis was done using SPSS statistical package (SPSS Inc., Chicago, IL, USA). Wilcoxon’s matched pairs signed rank test were used to measure the changes from baseline of ocular inflammation and ocular attacks. Variance analysis (ANOVA) for repeated measures was used to measure the changes of VA. P-values < 0.05 were accepted as significant.

### Results

Twelve patients were included in the study. The demographics and clinical characteristics of the patients are summarized in the Table 1.

At 54-week visit, the number of ocular attacks decreased from 40 before treatment to 5 during the drug administration period (P < 0.001), and 9/12 (75%) patients achieved a complete remission of uveoretinitis with corticosteroid cessation at week 30 (Table 2).

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<tr>
<th>Table 1. Baseline demographic, and concurrent clinical manifestations in 12 patients with BD and RPU.</th>
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<td>Patient (n)</td>
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<td>Male/female</td>
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<td>Ocular attacks before infliximab therapy (n)</td>
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<td>Mean visual acuity (24 eyes)</td>
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<td>BD concomitant manifestations</td>
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<td>Oral aphthosis</td>
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<td>Phlebitis</td>
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<td>CNS vasculitis</td>
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<td>Pseudofolliculitis</td>
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<td>Erythema nodosum</td>
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<th>Table 2. Baseline and after 54-week follow-up visual acuity, number of ocular attacks, ocular inflammation and retinal vasculitis scores</th>
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<td>Visual acuity</td>
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<td>Ocular attacks (n)</td>
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All of them showed a dramatic improvement of ocular inflammation after the first infusion. Six patients were in complete remission at 6-week visit, and three at 22-week visit. These three patients experienced one ocular attack each at weeks 6, 10 and 11, respectively.

Mean VA improved from 0.2 ± 0.8 to 0.5 ± 0.4 (P < 0.001) at the end of the treatment.

At 24-month visit, seven out of nine (78%) patients were still in remission. The other two patients experienced two flares of uveitis each, at month 1 and 3 and 2 and 5, respectively. They were treated again with prednisolone 0.5 mg/kg/day and three consecutive infusions of infliximab 5 mg/kg with complete remission.

Concurrent clinical manifestations of BD completely remitted after three infusions, with no relapse during the follow-up with the exception of oral ulcers, which recurred in two patients with three and four episodes, respectively.

One patient had a partial remission with reduction of inflammatory ocular involvement from score 4 to 1 and retinal vasculitis score from 2 to 1. During the treatment period this patient experienced two ocular attacks at weeks 22 and 30. These episodes remitted after prednisolone dose increasing and additional infliximab infusions at the dose of 10 mg/kg.

Finally, 2/12 (17%) patients showed no improvement of uveitis after the third infliximab infusion and withdrew from the study as dictated by the study protocol.

Headache malaise and mild hypotension rapidly resolving by reducing the infusion rate were recorded in three patients. Minor upper respiratory tract infections were observed in four patients, with resolution after a few days of wide spectrum antibiotic therapy.

Otherwise, infliximab therapy was well tolerated with no serious AEs.
ANA positivity with anti-dsDNA resulted in 2/12 (17%) patients, without any signs and/or symptoms of a lupus-like syndrome over the follow-up.

**Discussion**

In addition to corticosteroids, colchicine and all available immunosuppressive and cytotoxic drugs have been employed to treat the acute phase of uveoretinitis of BD and to prevent recurrences [17–23]. However, these drugs were efficacious to arrest the disease progression in ~50–70% of patients [24]. Better results have been obtained using interferon-α2a. In a recent open-label study on 50 BD patients with uveitis treated with interferon-α2a a response rate of 92% was observed at week 52, with a significant improvement of visual acuity and remission of extraocular manifestations, except oral ulcers [25]. The clinical response was achieved in 50% of the patients at week 24, with progressive increasing of the percentage of responders to 90% over the following weeks.

To date, the efficacy of infliximab therapy at the dose of 5 mg/kg on refractory posterior uveitis of BD has been observed in sporadic case reports [12, 13, 26, 27], and in several open-label, short-term studies on small clinical series [11, 28–30]. Patients received 1–3 infliximab infusions, and additional infusions were administered in case of relapse. All these papers evidenced two main results: first, infliximab was effective in controlling the acute phase of inflammatory process of uvea and retinal vasculitis in the majority of the patients; second, infliximab was characterized by a rapid efficacy with marked improvement of ocular attacks after the first infusion and remission after the third.

These preliminary results have been recently confirmed by two additional open studies of 14 and 32 week duration [10, 31]. Ohno et al. [10] reported the efficacy of infliximab, infused at week 0, 2, 6, 10, to reduce the risk of ocular attacks in 13 patients followed up for 14 weeks. Sifakis et al. [31] treated 15 BD patients with refractory posterior uveitis with infliximab at the dose of 5 mg/kg for 24 weeks. At week 32 visit, 60% of patients achieved a complete remission with improvement of VA and reduction of the mean number of relapses.

In our study, patients received multiple infusions of infliximab until week 54 and successively followed up for 12 months. Confirming previous results, six out of twelve patients experienced a sustained remission with no disease flare during the 54-week treatment period, and three had one ocular attack each. Disease activity was completely suppressed and corticosteroid withdrawal was possible in all nine patients. Of these, seven patients were still in remission 12 months after the drug suspension at the last follow-up visit.

The two patients who experienced relapses during the drug-free follow-up period were successfully treated with additional infusions of infliximab.

In keeping with previous reports [10, 11, 29–33], also in our patients infliximab was rapidly effective with dramatic improvement of ocular inflammatory changes after one infusion and with sustained efficacy throughout the whole treatment period. In addition, other concurrent clinical manifestations of BD responded as well.

Of the remaining patients, one had a partial response and two patients did not respond at all. We have no reasonable explanation of treatment failure in these patients. However, a similar percentage of non-responders was observed in other studies [10, 31], and it could be related to a more severe disease or to an insufficient administered dose. We did not test anti-infliximab antibody production which may account for treatment failure in our patients. However, the two patients did not respond to the initial three infusions, and it seems unlikely to relate this failure to anti-infliximab antibody development that is usually responsible for drug efficacy loss over long-term treatment.

As regards the safety profile, in keeping with other reports [10, 11, 27–33], long-term infliximab therapy was well-tolerated with minor infusion-related reactions and no serious AEs.

The lower response rate observed in our study with respect to that observed in patients treated with Interferon-α2a [25] may be explained by a more severe disease in our clinical series, due to a different selection of patients. Differently from our study where infliximab was administered to patients with uveoretinitis resistant to corticosteroids and to at least one immunosuppressant, 11 out of 50 (22%) patients treated by Kotter et al. [25] had received corticosteroid therapy alone, and 3 (6%) had not been previously treated at all.

According to the literature data [10–12, 27–33], the results of our study show that infliximab compared with Interferon-α2a may offer some advantages in terms of response time and tolerability. In all reports infliximab was well tolerated with no serious adverse events, whereas side effects were frequent in patients treated with Interferon-α2a [25].

In summary, the results of present study confirm that infliximab is rapidly effective in a high proportion of patients with BD and refractory posterior uveitis. Moreover, our study suggests that long-term administration of the drug may be helpful to prevent ocular attacks in patients with BD.

**Rheumatology key messages**

- Infliximab is effective to induce the remission of refractory uveitis in a higher proportion of patients with BD.
- Infliximab is effective to significantly reduce the number of ocular attacks in patients with BD.

The authors have declared no conflicts of interest.

**References**