Infliximab in the treatment of posterior uveitis in Behçet’s disease
Long term follow up in four patients

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Summary

Objective To evaluate the efficacy of infliximab as adjuvant therapy for refractory uveitis in Behçet’s disease.

Methods Retrospective evaluation of 4 patients with Behçet’s disease and severe uveitis, refractory to conventional corticosteroid and immunosuppressant regimens, to which infliximab (anti-tumor necrosis factor-alpha (TNFα) antibodies) was added. The outcome measures were intraocular inflammation, visual acuity, reduction of daily corticosteroid dose, and adverse effects.

Results The mean follow-up period was 11 months (range: 2–29 months). Patients received a mean of 8 (range: 3–16) infliximab infusions. TNFα blockade with infliximab was effective for 2 of our 4 patients: the effect for them was rapid but transient. One patient experienced a thoracic herpes zoster, a severe adverse effect not previously reported.

Conclusions Response to infliximab was variable in patients with Behçet’s disease for whom conventional immunosuppression had failed. Infliximab allowed the daily corticosteroid dose to be reduced for some patients but required repeated infusions.

Behçet’s disease is a chronic inflammatory disorder. Its diagnosis is based on recurrent oral ulceration associated with at least 2 of the following: recurrent genital ulceration, eye involvement, skin lesions and a positive pathergy test (sensitivity: 91%, specificity: 96%)1. Eye involvement is the most frequent cause of complications and leads to blindness in 25% of those affected2. Although the etiology of Behçet’s disease remains unknown, an abnormal T-cell response to ocular antigens, producing tumor necrosis factor-alpha (TNFα), in particular, plays a key role in the pathogenesis of its associated uveitis3. Treatment of severe Behçet’s disease consists of suppressing this immune response. Several immunosuppressive agents are used: corticosteroids, azathioprine, cyclosporin A, interferon-alpha, chlorambucil, cyclophosphamide, methotrexate, and mycophenolate mofetil4. Infliximab, a humanized mouse monoclonal antibody directed against TNFα, is a more precisely targeted immunomodulatory agent widely prescribed for other autoimmune immune diseases, including rheumatoid arthritis, Crohn’s disease and, more recently, rheumatoid spondylitis, psoriasis and systemic vasculitis. One report suggests that infliximab is effective against resistant Behçet uveitis5.
We report our experience with infliximab in 4 patients with Behçet’s disease and refractory relapsing posterior uveitis.

**Methods**

This study retrospectively analyzed the medical files of the 4 patients with Behçet’s disease and severe uveitis in our center who received infliximab from October 2001 through March 2004.

Criteria for diagnosis were those defined by the International Study Group for Behçet’s disease, recurrent oral ulcers associated with at least 2 of the following criteria: recurrent genital ulcerations, eye involvement, skin lesions and a positive pathergy test. Severe uveitis was defined as eye inflammation of the posterior segment, that is, macular edema, papillary edema, retinal vasculitis or vitreitis so severe that the fundus could not be examined. Best visual acuity was measured with the Snellen scale, ranging from 0/10 to 10/10.

Patients received infliximab treatment if they had posterior uveitis resistant to systemic corticotherapy and a concomitant immunosuppressive agent known to be effective in Behçet’s disease. Infliximab was used as an alternative adjuvant therapy when corticosteroid pulses failed to obtain a rapid response, that is, it was given in addition to current therapy. The infliximab dose was 5 mg/kg per intravenous infusion, with the first 3 infusions administered on days 0, 15, and 45.

Visual acuity, slit lamp microscopy, fundus and physical examinations preceded each new infliximab infusion.

The efficacy of infliximab was evaluated within 2 weeks of the third infusion. Partial remission was defined as improvement of visual acuity by at least 1/10 and regression of posterior inflammation, that is, attenuation of the previously observed fundus abnormalities. Failure to respond was defined as no change after 3 infusions, and infliximab treatment was then discontinued. Infusions continued every 2 months for patients in partial remission. Visual acuity, ocular inflammation, and reduction of concomitant immunosuppression were evaluated regularly. Systemic or ocular complications occurring under infliximab were recorded.

**Results**

Table 1 summarizes the baseline clinical data and outcomes for each patient. All 4 patients, 3 women and 1 man, had Behçet’s disease with severe posterior uveitis. They had been treated in our departments for a mean of 2 years before infliximab treatment began. Their mean age was 32 years (range: 24-39 years). Infliximab was infused a mean of 8 times (range: 3-16). Seven eyes of 4 patients were studied because patient 3 was already blind in one eye. Patients 3 and 4 had no improvement after the third infusion. Patient 3’s visual acuity deteriorated by 2/10 and she required 60 mg daily of prednisone, later administered with interferon and then mycophenolate mofetil, to treat this problem.

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Sex</th>
<th>Fundus features at baseline</th>
<th>Prior treatments</th>
<th>Daily therapy before infliximab</th>
<th>No. of infliximab infusions</th>
<th>Follow-up (mo)</th>
<th>Partial remission after 3 infusions</th>
<th>Daily therapy after infliximab</th>
<th>Visual acuity after infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24/F</td>
<td>Bilateral vitreitis, right papillary edema</td>
<td>AZA: 2 mg/kg/d; MTX: 0.3 mg/kg/ivk</td>
<td>PRED (40 mg/d), COLC, ASA</td>
<td>9</td>
<td>12</td>
<td>Yes</td>
<td>PRED (9 mg/d), COLC: 1 mg/kg/d, ASA: 100 mg/d, CYC: 0.6 gr/m/month, MMF: 2 griday</td>
<td>5/10 right 4/10 left 10/10 right 10/10 left</td>
</tr>
<tr>
<td>2</td>
<td>27/F</td>
<td>Bilateral vitreitis and macular edema, right hypopyon</td>
<td>IFNα</td>
<td>PRED (50 mg/d), COLC: 1 mg/d, ASA: 100 mg/d, AZA (100 mg/d)</td>
<td>16</td>
<td>29</td>
<td>Yes</td>
<td>PRED (10 mg/d), COLC1 mg/d, ASA: 100 mg/d, AZA (2 mg/kg/d)</td>
<td>Hand motions right 5/10 left 6/10 right 10/10 left</td>
</tr>
<tr>
<td>3</td>
<td>39/F</td>
<td>Right macular edema; left blindness</td>
<td>CYC</td>
<td>PRED (35 mg/d), COLC: 1 mg/d</td>
<td>3</td>
<td>2</td>
<td>No</td>
<td>IV MPRED: 1 grid, PRED (60 mg/d), CYC</td>
<td>3/10 right 0/10 left 1/10 right 8/10 left</td>
</tr>
<tr>
<td>4</td>
<td>39/M</td>
<td>Right vasculitis</td>
<td>MTX: 0.3 mg/kg/ivk, IFNα: 3 MU 3 times/ivk, AZA: 2 mg/kg/d, COLC: 1 mg/d</td>
<td>PRED (20 mg/d), laterobulbar PRED injections</td>
<td>3</td>
<td>3</td>
<td>No</td>
<td>PRED (15 mg/d), MMF: 2 grid</td>
<td>10/10 right 10/10 left 10/10 right 10/10 left</td>
</tr>
</tbody>
</table>

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uveitis deterioration. Papillary and macular edema were present after the third infusion. Patient 4’s visual acuity did not change but he suffered 2 relapses of uveitis with vitreitis. Infliximab was discontinued for these 2 patients. Patients 1 and 2 achieved partial remissions. Their visual acuity improved dramatically (table 1), and their daily prednisone doses could be sharply reduced. Patient 1 no longer had fundus abnormalities after the third infusion. She continued to receive infliximab infusions every 2 months throughout the follow-up. Patient 2’s fundus abnormalities had regressed after the third infusion, but the uveitis relapsed when the 6th infusion was delayed to 10 weeks. Twelve months after starting infliximab, she developed severe thoracic herpes zoster, which responded favorably to valaciclovir. Finally, 18 months after starting infliximab, bilateral subcapsular cataracts appeared, attributed to the corticosteroid treatment; she underwent successful cataract surgery. She received infliximab every 6 weeks because uveitis recurred when it was infused at 2-month intervals. When last seen, both patients were still on combined regimens including infliximab (table 1) and they no longer had any fundus abnormalities. Infliximab induced short-term remission of non-ocular manifestations of the disease in all patients.

**Discussion**

This is the first study to present long-term follow-up of a homogeneous group of patients with Behçet’s disease and severe posterior uveitis treated with infliximab. Sfikakis et al. were the first to prescribe infliximab to 5 patients with Behçet’s disease but they administered only a single infusion and follow-up lasted 14 days. Ocular inflammation persisted 7 days after treatment in all patients. Another study concerned 5 patients with uveitis, 3 of whom had Behçet’s disease; follow-up was 6 months. Four of the 5 patients achieved remission and 1 developed ocular and systemic tuberculosis, as a side effect of infliximab. A more recent investigation included 7 patients with refractory uveitis and scleritis, but none had Behçet’s disease. With a mean follow-up of 12 months, 5 patients entered remission and 1 had developed a hypersensitivity reaction. The most recent published study includes 4 cases of refractory panuveitis due to Behçet’s disease. Infliximab was reported to be effective in all cases. Our 4 patients were treated for 2 to 29 months. Patients 1 and 2 responded favorably to infliximab; however, without repeated infusions, relapses of the uveitis occurred. Adjuvant infliximab also allowed us to reduce the daily corticosteroid dose for both markedly. Patient 2’s severe relapse occurred after an abnormally long interval before the 6th infusion, and she required maintenance infusions every 6 weeks. Patient n°2 also developed severe thoracic herpes zoster, attributed to the combination of treatments (steroids, infliximab and several previous immunosuppressants). The other 2 patients did not respond to adjuvant infliximab. In our series infliximab was effective in 50% of the cases, a much lower rate than in previous reports. The principal disadvantage of infliximab infusions in our test conditions is the short duration of effect, but the high cost of this agent must also be kept in mind. Infliximab could be included as part of a therapeutic regimen for Behçet’s disease but cannot be given alone. Long-term studies with more patients are needed to determine the role of other agents.

**WHAT IS ALREADY KNOWN**

- Infliximab can be effective to treat refractory uveitis and scleritis.
- In severe cases of uveitis in Behçet’s disease, a study reported efficiency of infliximab after a single injection and a short follow-up of 14 days.
- Another study reported efficiency of infliximab in 4 patients with severe uveitis due to Behçet’s disease. Infliximab was reported to be effective in all cases.

**WHAT THIS ARTICLE ADDS**

- In our series, infliximab was effective in 50% of the cases, a much lower rate than in previous reports.
- Infliximab could be included as part of therapeutic regimen for Behçet’s disease.


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**References**


