Infliximab Therapy for the Treatment of Refractory Ocular Inflammatory Disease

Lucia Sobrin, MD; Eva C. Kim, MD; William Christen, PhD; Thekla Papadaki, MD; Erik Letko, MD; C. Stephen Foster, MD

Objective: To report the outcomes of infliximab therapy in the treatment of ocular inflammatory disease refractory to traditional immunomodulatory therapy (IMT).

Methods: We retrospectively reviewed the medical records of 27 patients. All patients had noninfectious ocular inflammatory disease refractory to traditional IMT and received 5 mg/kg of infliximab at 2-week to 8-week intervals. Main outcome measures were clinical response, reduction in concomitant IMT, and adverse effects. Cumulative incidences of inflammation control and vision change were calculated using life-table methods.

Results: Twenty-one patients experienced sustained improvement in inflammation with their initial course of infliximab therapy. Cumulative incidence of inflammation resolution at 12 months was greater than 90%. Sixteen patients were able to decrease the dose of their concomitant IMT medication or stop all other IMT. Four patients were able to discontinue all other IMT while receiving infliximab therapy. Three patients with scleritis were eventually able to remain inflammation-free while not taking any medication. At 12 months, 56% and 65% of left and right eyes, respectively, showed visual acuity improvement by 2 or more Snellen lines. Only 1 patient developed an adverse event requiring therapy discontinuation.

Conclusions: We found a high rate of ocular inflammation control with infliximab therapy. The incidence of adverse effects in this study was low.

Arch Ophthalmol. 2007;125(7):895-900

Ocular inflammatory disease includes a wide spectrum of conditions such as chronic cicatriz- ing conjunctivitis, scleritis, and uveitis. Treatment of these sight-threatening problems has been greatly advanced with the application of traditional immunomodulatory therapy (IMT), including antimetabolites and alkylating agents. However, a small yet significant proportion of patients remain refractory to conventional IMT. The recent development of biologic agents that target specific cytokines holds promise for additional effective treatments.

Tumor necrosis factor α (TNF-α) is a cytokine and inflammatory mediator in animal models of uveitis. Its blockade is associated with decreased ocular inflammation in these animal models. In addition, TNF-α has been found in higher levels in the sera and aqueous humor of patients with uveitis. These findings form the rationale for the use of anti-TNF-α biologic agents in ocular inflammatory diseases.

Infliximab, a monoclonal antibody to TNF-α, is a biologic agent that has been approved for use in rheumatoid arthritis, Crohn disease, and ankylosing spondilitis. Many centers have used infliximab off-label for the treatment of different types of ocular inflammation with initially promising results. In this report, we describe our experience with the use of infliximab in patients with ocular inflammatory disease resistant to traditional IMT.

METHODS

The Human Studies Committee of the Massachusetts Eye and Ear Infirmary approved the retrospective data review for this study with waiver of informed consent. Cases were consecutive patients with ocular inflammatory disease refractory to traditional IMT who received intravenous infliximab (Remicade; Centocor, Inc, Malvern, Pennsylvania) between January 1, 2001, and March 30, 2006, while under the care of 1 of us (C.S.F.) at a uveitis referral center. Patients at this center are treated with a stepladder approach to IMT, which typically starts with an antimetabolite, such as methotrexate, or a signal transduction inhibitor, such as cyclosporine. If pa-
The clinical data for each patient are summarized in Table 1. The ocular diagnoses included scleritis (n=8), scleritis and anterior uveitis (n=1), scleritis and panuveitis (n=1), anterior uveitis (n=8), panuveitis (n=3), retinal vasculitis and panuveitis (n=5), and OCP (n=1). Twenty-one patients had underlying systemic diagnoses, which included rheumatoid arthritis (n=2), juvenile idiopathic arthritis (n=5), ankylosing spondylitis (n=2), Behcet disease (n=6), reactive arthritis (n=2), relapsing polychondritis (n=1), Crohn disease (n=1), psoriasis (n=1), and mucous membrane pemphigoid (n=1). Five of these patients with systemic disease were HLA-B27 positive. The mean patient age was 37.3 years (range, 6-66 years). The mean number of infliximab infusions was 15.6 (range, 4-45), and the mean follow-up time from the first infusion was 25.6 months (range, 4-62 months). While all patients had active ocular inflammation, patients 1, 11, 14, 16, and 17 received infliximab primarily for joint inflammation and the remaining 22 patients received infliximab primarily for ocular inflammation. The medications in Table 1 reflect the IMT regimen immediately prior to infliximab initiation. It does not include all of the IMT medications that each patient might have tried and failed previously. Patients 11, 14, 16, and 17 were only treated with methotrexate prior to the introduction of infliximab therapy; the infliximab was prescribed by their rheumatologists for joint disease and controlled their ocular inflammation before the usual stepladder approach to IMT could be continued for their eyes. Patient 23 was changed from methotrexate therapy directly to infliximab therapy because of early reports about Behcet disease responding well to anti–TNF-α therapy and because his serum TNF-α level was quite elevated at 27 pg/mL (reference range, 0-8.1 pg/mL). Tumor necrosis factor α levels were not checked in most patients and this is the only instance where the TNF-α level impacted therapy. Patients 2 and 18 were receiving monotherapy with methotrexate and prednisone, respectively, because of intolerance to multiple IMT medications.

Twenty-one of 27 patients achieved ocular inflammation control with the initial addition of infliximab therapy to their IMT regimens. Two additional patients (patients 3 and 22) achieved control of inflammation after an interval of alkylating agent therapy. Patient 3 had ongoing inflammation with her first trial of infliximab therapy, required intravenous cyclophosphamide therapy for several months, and then went back to infliximab and methotrexate therapy with good inflammation control since then. Patient 22 had recurrent inflammation while taking infliximab, requiring intravenous steroids followed by oral chlorambucil therapy for 4 months. After this "rescue" therapy, he has been inflammation-free while taking infliximab, cyclosporine, and prednisone for 8 months.

After achieving suppression of ocular inflammation, we were able to reduce either the dosage of a particular IMT medication or the number of IMT drugs for 9 patients.
Table 1. Clinical Data of Patients Treated With Infliximab

<table>
<thead>
<tr>
<th>Patient No./Age/Sex, y</th>
<th>Ocular and Systemic Diagnoses</th>
<th>Therapy Before Infliximab</th>
<th>Current Therapy</th>
<th>No. of Infusions</th>
<th>Follow-up, mo</th>
<th>Visual Acuity Before Infliximab Therapy</th>
<th>Visual Acuity After Infliximab Therapy</th>
<th>Inflammation Before Infliximab Therapy</th>
<th>Inflammation After Infliximab Therapy</th>
<th>Status at Last Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/44/M</td>
<td>Scleritis OD, AS, HLA-B27 positive</td>
<td>PRED, AZA, leflunomide</td>
<td>INF, AZA, leflunomide</td>
<td>16</td>
<td>24</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>2 injection OD, quiet OS</td>
<td>Quiet OU</td>
<td>Nonresponder; unable to reduce concurrent IMT</td>
</tr>
<tr>
<td>2/56/M</td>
<td>Nodular scleritis OU, reactive arthritis</td>
<td>MTX</td>
<td>MTX</td>
<td>14</td>
<td>17</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>1 injection OU</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>3/60/F</td>
<td>Scleritis OU, RA</td>
<td>CYC, MTX</td>
<td>INF, MTX</td>
<td>9</td>
<td>24</td>
<td>20/30 OU</td>
<td>20/30 OU</td>
<td>1 injection OU</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>3/63/F</td>
<td>Scleritis OS, RA</td>
<td>CYC</td>
<td>None</td>
<td>6</td>
<td>12</td>
<td>CF OD, 20/25 OS</td>
<td>CF OD, 20/25 OS</td>
<td>Quiet OD, Quiet OU</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>5/63/M</td>
<td>Scleritis OU, relapsing polychondritis</td>
<td>AZA, PRED, hydroxychloroquine sulfate</td>
<td>AZA, PRED</td>
<td>8</td>
<td>8</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>Quiet OD, Quiet OS</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>6/48/F</td>
<td>Scleritis OD</td>
<td>ETA, PRED</td>
<td>MMF, PRED</td>
<td>7</td>
<td>49</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>2 injection OD, quiet OS</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>7/54/F</td>
<td>Scleritis OU</td>
<td>PRED, DAC</td>
<td>None</td>
<td>7</td>
<td>26</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>2 injection OD, quiet OS</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>8/66/M</td>
<td>Nodular scleritis OU</td>
<td>CYC</td>
<td>None</td>
<td>16</td>
<td>27</td>
<td>20/20 OD, 20/20 OD, 20/20 OS</td>
<td>20/20 OD</td>
<td>3 injection OU, Quiet OU</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>9/28/M</td>
<td>Scleritis OU, panuveitis OU, Crohn disease</td>
<td>MMF, sirolimus</td>
<td>INF, MMF, sirolimus</td>
<td>9</td>
<td>9</td>
<td>20/50 OD, 20/30 OD</td>
<td>20/50 OD</td>
<td>1 injection OD, QUIET OS</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>11/9/M</td>
<td>Anterior uveitis OU, JIA</td>
<td>PRED, MTX</td>
<td>MMF</td>
<td>15</td>
<td>27</td>
<td>20/20 OU</td>
<td>20/20 OD, 20/25 OS</td>
<td>Quiet OD, QUIET OD, QUIET OS</td>
<td>Quiet OD, QUIET OD, QUIET OS</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>12/16/F</td>
<td>Anterior uveitis OU, JIA</td>
<td>CYC, PRED</td>
<td>INF</td>
<td>28</td>
<td>37</td>
<td>20/400 OD, 20/30 OD</td>
<td>20/100 OD</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>13/15/F</td>
<td>Anterior uveitis OU, JIA</td>
<td>CSA, MMF</td>
<td>INF, MTX</td>
<td>12</td>
<td>16</td>
<td>20/20 OD</td>
<td>20/20 OD, 20/20 OS</td>
<td>QUIET OD, QUIET OD</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>14/20/M</td>
<td>Anterior uveitis OU, JIA</td>
<td>MTX</td>
<td>INF, MTX</td>
<td>20</td>
<td>25</td>
<td>20/20 OD, 20/25 OS</td>
<td>20/20 OD, 20/25 OS</td>
<td>Quiet OD, QUIET OD, QUIET OD</td>
<td>Quiet OU</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>15/35/M</td>
<td>Anterior uveitis OD, JIA, HLA-B27 positive</td>
<td>ETA, MTX, PRED</td>
<td>INF, MTX, PRED</td>
<td>12</td>
<td>12</td>
<td>20/30 OD, LP OS</td>
<td>20/30 OD, LP OS</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>16/36/F</td>
<td>Anterior uveitis OU, JIA, HLA-B27 positive</td>
<td>MTX</td>
<td>INF</td>
<td>45</td>
<td>62</td>
<td>20/20 OU</td>
<td>20/15 OU</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; able to reduce concurrent IMT</td>
</tr>
<tr>
<td>17/49/M</td>
<td>Anterior uveitis OD, reactive arthritis, HLA-B27 positive</td>
<td>ETA, MTX, MMF</td>
<td>ETA, MTX</td>
<td>10</td>
<td>29</td>
<td>20/20 OD</td>
<td>20/20 OD</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>18/16/F</td>
<td>Anterior uveitis OU, psoriasis</td>
<td>PRED</td>
<td>PRED</td>
<td>10</td>
<td>26</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>19/27/M</td>
<td>Panuveitis OU</td>
<td>MMF</td>
<td>MMF</td>
<td>4</td>
<td>33</td>
<td>20/20 OU</td>
<td>20/20 OU</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>20/5/M</td>
<td>Panuveitis OU</td>
<td>CSA, MTX</td>
<td>INF</td>
<td>20</td>
<td>22</td>
<td>20/70 OD, 20/70 OD</td>
<td>20/15 OD</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
<tr>
<td>21/59/M</td>
<td>Panuveitis OS, BD</td>
<td>PRED, CYC</td>
<td>PRED</td>
<td>9</td>
<td>29</td>
<td>20/20 OD, 20/70 OD</td>
<td>20/20 OD, 20/30 OD</td>
<td>QUIET OD, QUIET OD, QUIET OD</td>
<td>QUIET OD</td>
<td>Nonresponder; initial control of inflammation with INF but then relapsed</td>
</tr>
</tbody>
</table>
(patients 2, 3, 5, 13, 15, 22, 23, 24, and 27). Seven patients (patients 4, 7, 8, 12, 16, 20, and 25) were able to discontinue all other IMT while receiving only infliximab therapy. Patient 9 received 4 infliximab infusions and then was noncompliant with visits. When he returned for care, his inflammation was controlled after not taking any medications for 7 months. The remaining 6 patients were unable to decrease either the dosage or number of IMT drugs.

Four patients did not achieve sustained inflammation control. Patient 17 responded so well to infliximab therapy initially that his methotrexate therapy was discontinued. Severe inflammation returned after 3 months, prompting reinstitution of methotrexate therapy. Control of his inflammation was eventually achieved with etanercept and methotrexate therapy without infliximab use. Patient 21 never achieved inflammation control while taking infliximab. Patients 11 and 18 achieved inflammation control initially but it eventually recurred while receiving infliximab.

Life-table methods were used to calculate cumulative incidences of inflammation control and vision change at 12 months (Table 2). Among eyes with inflammation at the first infusion (22 right eyes, 21 left eyes), greater than 90% showed complete resolution of inflammation at 12 months. Among eyes with a visual acuity of 20/30 or worse at the first infusion (10 right eyes, 13 left eyes), cumulative incidence of improvement in visual acuity by
The rates of ocular inflammatory control with the initial addition of infliximab therapy in this study are 78% of patients and 81.4% of eyes, which are similar to the response rates reported in previous studies. After additional courses of alkylating agents in 2 patients, the rates of inflammation control increased to 85% (23 of 27 patients) and 90.7% (39 of 43 eyes), respectively. This effect was sustained over a mean follow-up of 25.6 months, to our knowledge, the longest of any study published to date. The majority of our patients could not be included in this analysis because their visual acuity was 20/30 or better at the first infusion. This reflects our clinical approach, which is to generally treat patients with ocular inflammation before their vision is compromised. Life-table analysis for a visual acuity decrease indicated that less than 15% of patients had a drop in visual acuity by 2 or more lines at 1 year. This analysis included patients who failed infliximab therapy and had ongoing inflammation.

Two patients who initially had inflammation recurrence while receiving infliximab therapy received a course of alkylating medication and were able to resume infliximab therapy with good inflammation control thereafter. Patient 3 received intravenous cyclophosphamide therapy for 6 months and patient 22 received 4 months of chlorambucil therapy. One relapse while taking infliximab should not eliminate it from the ocular immunologist's armamentarium for that patient. It may be useful as a maintenance drug after the acute episode of inflammation is quelled. In addition, given the recent finding that combination therapy with cyclophosphamide and etanercept, another anti-TNF-α biologic agent, may heighten the risk of cancer beyond that observed with cyclophosphamide therapy alone in the treatment of Wegener granulomatosis, patients should not be treated concomitantly with an alkylating agent and biologic agent until further information is available. In this study of Wegener granulomatosis, however, prior therapy with cyclophosphamide did not affect the incidence of malignancy.

In contrast with the recent finding of a relatively high rate of adverse events in a prospective trial of infliximab therapy, our retrospective review included only 1 adverse event necessitating therapy discontinuation. As the authors of the aforementioned prospective trial point out, the causality for several of the significant adverse events is unclear. Other studies have shown low rates of adverse events similar to those in our report. Drug-induced lupus reaction is the one significant adverse event that we observed; this has been previously reported in the ophthalmic and rheumatologic literature with use of infliximab. As with our patient, all the reported
cases of lupus-like syndrome in clinical trials and post-marketing surveillance have improved with therapy discontinuation.\textsuperscript{24} Our study included patients with a wide variety of ocular inflammatory conditions. Unlike other studies, we included patients with anterior uveitides of different etiologies as well as patients with posterior involvement. To our knowledge, this report includes the first published case of OCP treated with infliximab. Patient 27 reported subjective improvement of irritation and pain and had objective signs of improved inflammation after 8 infliximab infusions. Because of the control of his inflammation, he was able to undergo keratoprosthesis surgery, which led to visual acuity improvement from light perception to 20/100 in the eye that underwent surgery. To our knowledge, our study also includes the largest series of patients with scleritis published to date. All 10 of these patients with scleritis had inflammation control while taking infliximab. Patients with scleritis may be a subgroup of patients who respond well to infliximab therapy and who are more likely to achieve remission. A larger randomized trial would be necessary to further test these hypotheses.

Four of our patients are continuing to receive infliximab therapy without any concomitant IMT. Typically, patients are maintained on low-dose immunosuppressive therapy to prevent antibody production to infliximab. The patients who opted for monotherapy were all informed of the risk of antibody development and subsequent tachyphylaxis to infliximab use. Their desire to avoid immunosuppressive therapy and their good inflammation control while taking infliximab led them to make this choice. All these patients have maintained an excellent response to infliximab therapy, having received between 20 and 45 infusions. Monotherapy may be offered to patients with uveitis and may be efficacious over the long-term.

In our experience, the optimal maintenance infliximab dosing interval for patients with uveitis is shorter than the 8 weeks that has been reported for patients with diseases such as Crohn disease.\textsuperscript{8} We have found that every-month dosing in these patients eliminates “escape” of inflammation between treatments, and this schedule is well tolerated. Of the 5 patients in this series who were treated primarily by their rheumatologists for joint disease with a prolonging of intervals between infusions up to every 8 weeks, 3 were able to achieve ocular inflammation control.\textsuperscript{7}

We found infliximab therapy to be an efficacious biologic agent for the treatment of refractory ocular inflammation. There was a low incidence of adverse effects prompting discontinuation. This study, however, is limited by its retrospective nature, lack of a control group, relatively small number of patients, and limited follow-up period for some patients. Randomized controlled trials of infliximab therapy for patients with various subtypes of ocular inflammatory disease would be required to answer questions of efficacy and safety more definitively.

Submitted for Publication: June 10, 2006; final revision received November 20, 2006; accepted November 22, 2006.

Correspondence: C. Stephen Foster, MD, Massachusetts Eye Research and Surgery Institute, 5 Cambridge Center, Eighth floor, Cambridge, MA 02142 (fosters@uveitis.org).

Financial Disclosure: None reported.

REFERENCES