Neutralizing Tumor Necrosis Factor Activity Leads to Remission in Patients With Refractory Noninfectious Posterior Uveitis

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Objective: To evaluate the efficacy and safety of tumor necrosis factor (TNF) inhibition with the p55 TNF receptor fusion protein (TNFr-Ig) for severe sight-threatening noninfectious posterior segment intraocular inflammation.

Methods: Seventeen patients with refractory noninfectious posterior segment intraocular inflammation received TNFr-Ig by intravenous infusion in this nonrandomized, open-label, pilot study. The primary outcome measure was logMAR visual acuity. Secondary outcome measures were binocular indirect ophthalmoscopy score, cystoid macular edema, adverse effects, and vision-related (visual core module 1) and health-related (36-Item Short-Form Health Survey) quality of life.

Results: Within 1 month of TNFr-Ig therapy, 9 patients (53%) achieved at least a 2-line improvement in visual acuity, 8 (57%) of 14 patients with vitreous haze before treatment achieved an improvement in binocular indirect ophthalmoscopy score to 0, and macular edema resolved in 5 (56%) of 9 affected patients. Twelve (71%) of the patients achieved complete cessation of intraocular inflammation following TNFr-Ig therapy. A reduction in concomitant immunosuppression was possible for 11 patients (65%) following TNFr-Ig therapy. However, all but 1 patient required continuing adjuvant therapy during the response to TNFr-Ig, which had a median duration of 3 months. Adverse effects included mild infusion reaction in 3 patients and transient lymphocytopenia in 2 patients.

Conclusion: Therapy with TNFr-Ig was safe and effective for treating patients with sight-threatening noninfectious posterior segment intraocular inflammation resistant to conventional immunotherapy, but adjuvant immunosuppression and repeat infusions would be required to maintain long-term remission.


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in patients with other autoimmune diseases, such as rheumatoid arthritis and Crohn disease,15-18 and their recent successful use in patients with ocular Behçet disease.19 We report the use of TNFr-Ig in a phase 1/2 study in patients with PSII. The objectives of this study were to evaluate the efficacy and tolerability of short-term therapy with TNFr-Ig in patients with refractory noninfectious PSII and to estimate its impact on health-related quality of life (HQOL) and vision-related quality of life (VR-QOL).

**METHODS**

**PATIENTS**

Patients were recruited to this open-label, nonrandomized, pilot study of TNFr-Ig for PSII from 2 regional referral centers for uveitis in the United Kingdom, the Bristol Eye Hospital, Bristol, and the Aberdeen Royal Infirmary, Aberdeen. The study was approved by the ethics committees of each center, and informed consent was obtained from all patients. The inclusion criteria were chronic noninfectious sight-threatening PSII and treatment failure with prednisolone (>10-mg/d maintenance dosage) and at least 1 immunosuppressive agent, most commonly cyclosporine, because of either refractory disease or drug intolerance. Reasons for exclusion from the study were pregnancy, diabetes mellitus, renal disease, concurrent infection, and recent live vaccinations.

**TNFr-Ig THERAPY**

The TNFr-Ig molecule is a chimeric molecule comprising the extracellular domain of the human p55 TNF receptor fused to the hinge, CH1, and CH2, domains of the human IgG1 heavy chain; and was manufactured by the Therapeutic Antibody Centre, University of Oxford. This construct is similar to the one described by Peppel et al.20 The TNFr-Ig molecule inhibits human TNF-α function in vitro and is a potent antagonist of TNF-α in patients with EAU.12,13 An intravenous infusion of TNFr-Ig, 50 mg, in isotonic sodium chloride solution was administered over 4 hours. A second infusion of TNFr-Ig, 100 mg, was given to patients who responded to the first infusion but developed a sight-threatening relapse of intraocular inflammation within 3 months. Preexisting immunosuppression was maintained or reduced while the response to TNFr-Ig therapy was being evaluated. Antibody responses to TNFr-Ig were measured in patients’ serum samples before each treatment, at 2 weeks, and at 1, 2, 3, and 5 months after treatment by a sandwich enzyme-linked immunosorbent assay, as described elsewhere,21,22 with some modifications to improve reliability.

**CLINICAL ASSESSMENT**

A systemic and ophthalmic examination was undertaken immediately before TNFr-Ig therapy, at 2 and 4 weeks after therapy, and then at 4- to 6-week intervals according to clinical activity and response to treatment. The baseline assessment included a medical history, a general physical and ophthalmic examination, a blood pressure reading, a urinalysis, a chest x-ray film, and blood tests, including a complete blood cell count, a creatinine level test, liver function tests, a glucose level test, a urate level test, a C-reactive protein profile, and a lipid profile. Patients were examined at each follow-up visit for adverse effects and clinical response to TNFr-Ig therapy. The international Uveitis Scoring System was used to assess clinical disease activity, and lens opacities were graded using the Lens Opacities Classification System III.23,24

**QUALITY-OF-LIFE ASSESSMENT**

Three self-administered questionnaires were used to assess HQOL, VR-QOL, and adverse effects experienced before TNFr-Ig therapy and after 1, 3, and 6 months. Health-related quality of life was measured using the validated United Kingdom standard version of the 36-Item Short-Form Health Survey,25 which consists of 36 items grouped into 8 subscales to measure health, including physical functioning, social functioning, role limitations because of physical problems, role limitations because of emotional problems, mental health, energy/vitality, bodily pain, and general health perception. The 36-Item Short-Form Health Survey subscale scores range from 0% to 100%, with higher scores indicating better health. Vision-related quality of life was measured using the vision core module 1 (VCM1), a 10-item questionnaire that provides a subjective measure of concern regarding vision, with scores ranging from 0.0 (best score) to 5.0 (worst score), with 50 intervals.26 Finally, patients completed an adverse effect questionnaire that contained a comprehensive list of well-recognized adverse effects to immunosuppressive agents. This questionnaire, which addressed the overall effect of adverse effects on quality of life (asking “how much have these problems interfered with your quality of life?”), was scored from 0 (no adverse effects) to 5 (extreme adverse effects).

**OUTCOME MEASURES**

The primary outcome measure was best-corrected logMAR visual acuity measured at 4 m with the Early Treatment Diabetic Retinopathy Study chart, scored for individual letters. The chart was illuminated with an illumination unit (Lighthouse Chart Illumination Unit; Lighthouse International, New York, NY). Secondary outcome measures were binocular indirect ophthammoscopy (BIO) score, cystoid macular edema, Lens Opacities Classification System III grading of cataract, adverse effects, VR-QOL, and HQOL. True changes in visual acuity and BIO score following TNFr-Ig therapy were defined as an improvement in visual acuity of at least 2 lines (a decrease in the logMAR score of at least 0.2) or a decrease in the BIO score to 0 in either eye within 1 month of treatment. To evaluate the duration of response to TNFr-Ig, the end of the period of response was defined by a decrease in visual acuity of at least 2 lines or an increase in BIO score of at least 1 in either eye.

Statistical analysis was performed using the Wilcoxon signed rank test. A software program (Prism, version 3.02; GraphPad, San Diego, Calif) was used for all statistical calculations, and significance was attributed when P<.05.

**RESULTS**

**DEMOGRAPHIC AND CLINICAL CHARACTERISTICS**

Seventeen patients were enrolled in the study between June 1, 2001, and May 28, 2002. All patients who met the study enrollment criteria during this period agreed to participate. Their mean age was 43 years (range, 25-59 years), and 11 patients were women. The mean duration of uveitis at enrollment was 6 years (range, 0.5-12 years), and the mean follow-up after TNFr-Ig therapy was 8 months (range, 4-16 months), excluding 1 patient who was unavailable for follow-up after 1 month. Uveitis was bilateral in 14 patients and unilateral in 3 patients. Systemic diagnoses included tubulointerstitial nephritis and uveitis syndrome in 1 patient and Behçet disease in 2 pa-
Patients. Clinically apparent nonocular manifestations of systemic disease were absent in all patients. Prednisolone plus 1 other immunosuppressive agent failed in 3 patients before they received anti-TNF therapy, and at least triple therapy failed in the remainder of patients. Twelve patients received a single infusion of TNFr-Ig, 4 received 2 infusions, and 1 received a third infusion. Table 1 describes the clinical characteristics, systemic therapy before and after TNFr-Ig, and the outcome of treatment for each patient.

**CLINICAL EFFICACY OF TNFr-Ig**

Nine patients (53%) achieved a successful response to TNFr-Ig therapy according to the primary outcome measure, a 2-line improvement in visual acuity in 1 or both eyes within 1 month of treatment. In 8 (57%) of 14 patients with vitreous haze before treatment, presented by a BIO score of 1 or more, the BIO score improved to 0 in 1 or both eyes within 1 month of TNFr-Ig therapy; and macular edema resolved in 5 (36%) of 9 affected patients. Twelve (71%) of the patients achieved complete cessation of intraocular inflammation following TNFr-Ig therapy. The change in visual acuity and BIO score for worse and better eyes between baseline and 1 month following treatment is shown in Table 2. Figure 1 shows the improvement in visual acuity and BIO score for all uveitic eyes for 22 of 23 treatment periods during the 3 months following treatment (1 patient was unavailable for follow-up after 1 month). The median duration of response to TNFr-Ig was 3 months (range, 0.5-9 months), and 2 patients were still in remission at final follow-up at 9 months without any further increase in immunosuppression (Figure 2). A reduction in concomitant immunosuppression was possible for 11 patients (65%) following TNFr-Ig therapy (Table 1). Progression of cataract during the follow-up period occurred in 4 patients by 1 grade using the Lens Opacities Classification System III.

**SAFETY OF TNFr-Ig**

Three patients developed infusion-related adverse effects. Patient 7 complained of fatigue, headache, dizziness, and nausea during her first infusion, which got progressively worse during her second and third infusions, although not severe enough to warrant abandoning the treatment. Patient 12 complained of nausea and fatigue during the infusion, and patient 16 developed a mild hypersensitivity reaction characterized by a urticarial rash that resolved without treatment. Adverse effects reported in the days and weeks after TNFr-Ig therapy included mild headache in 2 patients, lymphocytopenia lasting less than 3 months in 2 patients concomitantly receiving tacrolimus or cyclosporine, nausea and vomiting 3 days after the infusion in 1 patient, and a severe itch approximately 1 month after the infusion in 3 patients.

**EFFECT OF TNFr-Ig ON QUALITY OF LIFE**

The median (interquartile range) VCM1 score decreased from 2.2 (1.6-3.0) at baseline to 1.7 (0.6-2.5), 1.7 (0.6-2.2), and 1.6 (0.3-2.4) at 1, 3, and 6 months, respectively, following TNFr-Ig therapy, indicating that a significant and sustained improvement in V-R-QOL occurred (P = .009, .02, and .03 for baseline vs 1-, 3-, and 6-month scores, respectively). Table 3 displays the 36-Item Short-Form Health Survey subscale scores, the VCM1 scores, and adverse effect scores at baseline and longitudinally during follow-up. The mental health and bodily pain subscale scores increased significantly following TNFr-Ig therapy (P = .04 and P = .006, respectively). A significant improvement in the self-assessed adverse effect score occurred following TNFr-Ig therapy, from a median (interquartile range) of 3.0 (2.0-3.0) at baseline to 2.5 (0.8-3.0) after 1 month (P = .04).

**ANTIBODY RESPONSES TO TNFr-Ig**

The results show that TNF blockade with TNFr-Ig is effective for the treatment of refractory noninfectious sight-threatening PSII. Within 1 month of anti-TNF therapy, 53% of the patients achieved an improvement in visual acuity of at least 2 lines, the primary outcome measure. Of the patients with vitreous haze, 57% experienced an improvement in BIO score to 0, and cystoid macular edema resolved in 56% of the patients when present. Therapy with TNFr-Ig induced complete remission in 71% of the patients. The efficacy of TNFr-Ig in patients with PSII was demonstrated not only by the improvement in clinical markers of intraocular inflammation but also by the improvement in HQOL and VR-QOL scores. Furthermore, the clinical benefit of repeat infusions was demonstrated in all 5 patients who received a second infusion.

The response to TNFr-Ig was maintained for a median of 3 months, and all but 3 patients relapsed during the follow-up period, indicating that while short-term control of ocular inflammation occurred, long-term remission through the induction of immune tolerance was generally not achieved. All but 1 patient continued to receive adjuvant immunosuppression following TNFr-Ig therapy, although at a lower dose in most patients. As in rheumatoid arthritis and Crohn disease, where the response to the anti-TNF monoclonal antibody infliximab is finite, repeat infusions of TNFr-Ig, and possibly adjuvant immunosuppression, would be required to maintain remission for the long-term. Nussenblatt and colleagues demonstrated that long-term therapy with an anti-interleukin 2 receptor monoclonal antibody (daclizumab) controlled PSII without the need for other immunosuppressive therapies. However, targeting cytokines...
Table 1. Patient Characteristics and Response to TNFr-Ig Therapy

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Diagnosis</th>
<th>TNFr-Ig Indication</th>
<th>Before TNFr-Ig Therapy</th>
<th>After TNFr-Ig Therapy</th>
<th>Duration of Response, mo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before/After</td>
<td>VA†</td>
<td>BIO Score†</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Treatment*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/44</td>
<td>Idiopathic retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 22 mg; CSA, 300 mg; MMF, 2 g</td>
<td>PRED, 8 mg; CSA, 300 mg; MMF, 2 g</td>
<td>0.7/0.12</td>
<td>0.54/0.1</td>
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<tr>
<td>2/F/55</td>
<td>TINU syndrome in both eyes</td>
<td>Drug toxicity</td>
<td>PRED, 10 mg None</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/F/53</td>
<td>Idiopathic intermediate uveitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 12 mg; TAC, 2 mg</td>
<td>PRED, 7.5 mg; TAC, 2 mg</td>
<td>0.1/0.6</td>
<td>0.00/0.5</td>
</tr>
<tr>
<td>4/F/31</td>
<td>Idiopathic posterior uveitis in both eyes</td>
<td>Drug toxicity</td>
<td>TAC, 2 mg</td>
<td>TAC, 2 mg</td>
<td>1.08/0.8</td>
<td>1.06/0.8</td>
</tr>
<tr>
<td>5/F/39</td>
<td>Behcet disease in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 20 mg; CSA, 200 mg</td>
<td>PRED, 12 mg; CSA, 250 mg</td>
<td>0.72/1.08</td>
<td>0.72/0.94</td>
</tr>
<tr>
<td>6/F/34</td>
<td>Multifocal choroiditis and panuveitis in left eye</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 60 mg; CSA, 200 mg</td>
<td>PRED, 12 mg; CSA, 250 mg</td>
<td>0.0/0.22</td>
<td>0.00/0.22</td>
</tr>
<tr>
<td>7/F/25</td>
<td>Idiopathic retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 20 mg; CSA, 400 mg; MTX, 10 mg/lc; MMF, 2 g</td>
<td>PRED, 10 mg; CSA, 400 mg; MTX, 10 mg/lc; MMF, 2 g</td>
<td>0.5/CF</td>
<td>0.04/0.84</td>
</tr>
<tr>
<td>8/M/35</td>
<td>Idiopathic retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 30 mg; TAC, 2 mg</td>
<td>PRED, 15 mg; TAC, 2 mg</td>
<td>CF/0.9</td>
<td>CF/0.34</td>
</tr>
<tr>
<td>9/F/42</td>
<td>Idiopathic intermediate uveitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 20 mg; MMF, 2 g</td>
<td>PRED, 20 mg; MMF, 2 g</td>
<td>0.0/0.7</td>
<td>−0.1/0.5</td>
</tr>
<tr>
<td>10/F/44</td>
<td>Idiopathic panuveitis with retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 20 mg; MMF, 1 g</td>
<td>PRED, 11 mg; MMF, 1 g</td>
<td>0.14/0.24</td>
<td>0.1/0.1</td>
</tr>
<tr>
<td>11/M/60</td>
<td>Sympathetic ophtalmia in left eye</td>
<td>Drug toxicity</td>
<td>PRED, 9 mg</td>
<td>PRED, 7.5 mg</td>
<td>0.14/†</td>
<td>−0.14‡</td>
</tr>
<tr>
<td>12/F/46</td>
<td>Idiopathic retinal vasculitis in both eyes</td>
<td>Drug toxicity</td>
<td>PRED, 5 mg; CSA, 400 mg</td>
<td>PRED, 5 mg</td>
<td>0.82/0.32</td>
<td>0.22/0.12</td>
</tr>
<tr>
<td>13/F/38</td>
<td>Idiopathic intermediate uveitis in both eyes</td>
<td>Drug toxicity</td>
<td>TAC, 4 mg</td>
<td>TAC, 3 mg</td>
<td>0.04/0.24</td>
<td>−0.14/−0.1</td>
</tr>
<tr>
<td>14/M/46</td>
<td>Idiopathic panuveitis with retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 12.5 mg; AZA, 150 mg</td>
<td>PRED, 12.5 mg; AZA, 150 mg</td>
<td>0.32/0.5</td>
<td>0.2/0.44</td>
</tr>
<tr>
<td>15/M/44</td>
<td>Idiopathic panuveitis and cataracts in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 15 mg; TAC, 5 mg</td>
<td>PRED, 20 mg; TAC, 5 mg</td>
<td>0.6/CF</td>
<td>0.62/CF</td>
</tr>
<tr>
<td>16/F/32</td>
<td>Behcet disease in right eye</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 18 mg; CSA, 250 mg</td>
<td>PRED, 13 mg; CSA, 250 mg</td>
<td>1.0/0.0</td>
<td>0.5/0.0</td>
</tr>
<tr>
<td>17/M/58</td>
<td>Idiopathic panuveitis and retinal vasculitis in both eyes</td>
<td>Refractory to treatment and drug toxicity</td>
<td>PRED, 60 mg; CSA, 250 mg; MMF, 1 g</td>
<td>PRED, 60 mg; CSA, 250 mg; MMF, 1 g</td>
<td>CF/0.62</td>
<td>1.06/0.36</td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; BIO, binocular indirect ophthalmoscopy; CF, counting fingers; CSA, cyclosporine; CYC, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; PRED, prednisolone; TAC, tacrolimus; TINU, tubulointerstitial nephritis and uveitis; TNFr-Ig, p55 tumor necrosis factor receptor fusion protein; VA, visual acuity.

*Data are given as value in the right eye/value in the left eye unless otherwise indicated.
†Data are given as value in the left eye only unless otherwise indicated.
in this way is only likely to provide short-term relief of inflammatory symptoms, rather than long-term disease modulation.

This contrasts with using the T-lymphocyte-depleting monoclonal antibody alemtuzumab (Campath-1H), which leads to long-term remission of ocular inflammatory disease after a 5-day course, possibly by inducing profound lymphocytopenia that on recovery allows the immune response to be “reset,” as confirmed in animal models.

Therapy with TNFr-Ig was well tolerated, and apart from 3 mild infusion-related reactions and temporary lymphocytopenia in 2 patients, no serious adverse effects occurred. A significant reduction in the self-reported adverse effect score following TNFr-Ig therapy, probably as a result of a reduction in concomitant immunosuppression, is further evidence that the treatment was largely uncomplicated. The clinical efficacy of TNFr-Ig in this cohort of patients is strengthened by the improvement in VCM1 scores following treatment, which paralleled the improvement in the clinical markers of ocular inflammation, visual acuity, and BIO score. Because the VCM1 is a validated instrument for measuring subjective concern regarding vision and has been used to measure VR-QOL in patients with uveitis, the results confirm that TNFr-Ig led to an objective and subjective improvement in ocular inflammation. Substantial improvements in the mental health and bodily pain subscales of the 36-Item Short-Form Health Survey also occurred, and these functional improvements lend further support to the efficacy of TNFr-Ig therapy.

The 3 infusion reactions that occurred were mild and short-lived. Two of these occurred during a repeat infusion following an uneventful first infusion, highlighting the possible immunogenicity of TNFr-Ig and the risk of increasing hypersensitivity reactions on repeat treatment. However, none of these infusion reactions were serious enough to warrant abandoning the treatment. Interestingly, mild injection site reactions and infusion reactions with 2 commercially available anti-TNF agents, etanercept and infliximab, are also common. Experience with infliximab in patients with rheumatoid arthritis and Crohn disease suggests that serious adverse effects with TNF blockade are rare, but recently, reactivation of tuberculosis has been highlighted as a rare but potentially fatal complication of treatment.

None of the patients in this study made high levels of specific antibodies in response to TNFr-Ig. Two patients had high responses in the antibody assay before treatment, indicating that they may have had natural antibodies that recognized TNFr-Ig. A weak and transient antibody response above the pretreatment levels was seen in 1 patient after each of 2 infusions, and a weak response, of doubtful significance, was seen in 1 other patient.

As a proinflammatory cytokine in experimental models, TNF-α activates T lymphocytes and macrophages and up-regulates endothelial adhesion molecules and other proinflammatory cytokines, playing a central part in the induction and maintenance of inflammation in autoimmune reactions. Consequently, following many clini-
Figure 2. Kaplan-Meier survival curve of the duration of response to p55 tumor necrosis factor receptor fusion protein (TNFr-Ig) therapy for 23 TNFr-Ig treatment episodes.

In summary, we have demonstrated that TNF-α blockade with TNFr-Ig was effective in rescuing patients with sight-threatening noninfectious PSII resistant to conventional immunotherapy. Therapy with TNFr-Ig not only led to the improvement of clinical markers of ocular inflammation but also to improved VRQOL and HQQOL. In addition to its use as a rescue therapy in this series, TNFr-Ig may have a role as a maintenance immunotherapy for patients who are refractory to conventional agents, but repeat infusions would be required to maintain long-term remission. The results of this pilot study support the need to assess anti-TNF therapies in longer-term treatment regimens for PSII in the context of randomized clinical trials.

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### REFERENCES


REFERENCES


Omission in Acknowledgments. In the Clinical Sciences article by Murphy et al titled “Neutralizing Tumor Necrosis Factor Activity Leads to Remission in Patients With Refractory Noninfectious Posterior Uveitis,” published in the June 2004 issue of the Archives (2004;122:845-851), an omission occurred in the Acknowledgments section on page 890. In that section, the following statement should have appeared as the second paragraph, immediately following the acceptance dates: “Drs Murphy and Greiner contributed equally to this study and stand as joint first authors.”