Anti-TNF- α therapy for uveitis: Behçet and beyond

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EDITORIAL

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In this issue, Benitez-del-Castillo *et al*¹ report six patients with refractory posterior uveitis (five Behçet and one sarcoidosis) who improved after anti-Tumour Necrosis Factor- α (anti-TNF- α) therapy. The authors state that at the end of the 3 years of follow-up, three out of the 10 eyes remaining in the study showed improved visual acuity, six remained the same, and only one eye lost one line of vision.

TNF- α is a pleiotropic cytokine produced by a number of cell types including macrophages and T-cells and has a crucial role in the pathogenesis of inflammation. It may induce expression of other proinflammatory cytokines and adhesion molecules, making it a prime target for specific immune therapy. This has led to the introduction of anti-TNF- α treatments that have been highly effective in patients with rheumatoid arthritis,² Crohn's disease,³ and ankylosing spondylitis,⁴ with consequent approval for their use by the National Institute for Clinical Excellence (NICE).

In experimental autoimmune uveoretinitis (EAU), the archetypal animal model of posterior uveitis, TNF- α has been shown to be an important cytokine in the development of tissue damage. Blockade of TNF- α activity alters the severity and course of the disease.⁵ Similar results are seen in the endotoxin-induced uveitis model.⁶

Human uveitis is regarded as a CD4 + T-cell-mediated autoimmune/autoinflammatory group of conditions. The mainstay of therapy for sight-threatening pan/posterior uveitis is systemic corticosteroid, often with the addition of one or two immunosuppressive agents, such as cyclosporine A, tacrolimus, azathioprine, methotrexate, and mycophenolate mofetil. In many patients, combinations of these drugs are effective at achieving disease control and maintaining or improving vision. Nevertheless,

there is a substantial cohort of uveitis patients who are refractory to more conventional immunosuppression. With the success of anti-TNF- α therapies in modulating other autoimmune diseases and experimental uveitis, plus evidence of raised TNF- α in ocular fluid and serum of uveitis patients,⁷ it is not surprising that anti-TNF- α agents are now being used in the management of human uveitis.

A number of commercial anti-TNF- α preparations are available. Etanercept (Enbrel, Wyeth) is a recombinant human TNFRp75-Fc fusion protein. It consists of the extracellular ligand-binding portion of two human 75 kDa (p75) TNF receptors (TNFRs) linked to the Fc portion of human IgG1. Conjugation of the receptors with human Fc extends the half-life of the receptors to approximate that of immunoglobulin. The dimer acts as a competitive inhibitor of TNF- α and prevents binding to the cell-surface TNFR. It is given twice weekly by subcutaneous injection. Infliximab (Remicade, Schering Plough) is a chimeric human/murine monoclonal antibody to TNF- α . It neutralises the effects of TNF- α by binding to the soluble and transmembrane forms and inhibits binding with its receptors. It is given at 2–4-weekly interval, at doses of 3–5 mg/kg by intravenous infusion.

Adalimumab (Humira, Abbott) is a newer preparation and is a 'fully' humanised anti-TNF- α antibody given subcutaneously at 2-weekly intervals. Both etanercept and infliximab have been shown to be effective in controlling inflammation in systemic autoimmune diseases. In addition, a p55 TNFR fusion protein has been developed but is not commercially available.

To date, there have been a number of published reports of anti-TNF- α treatment in uveitis. There are only a few studies on etanercept,^{8–10} mainly focusing on children with juvenile idiopathic arthritis-associated uveitis.^{8,9} To date, the evidence of benefit of etanercept is limited and not convincing. Nevertheless, a

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study on the use of the p55 TNFR fusion protein in uveitis is encouraging.¹¹ In 17 patients with refractory noninfectious posterior uveitis, nine patients (53%) achieved at least a 2-line improvement in visual acuity, with reduction of vitreous haze and macular oedema in almost 60% of patients. A reduction of concomitant immunosuppressive therapy was possible in 11 patients (65%).

The volume of the literature is larger for infliximab but comprises mainly open, uncontrolled case series or single case reports,^{12–24} the majority treating patients with Behçet's disease (BD). Despite the low hierarchy of evidence of these studies, most reports have shown a dramatic and lasting improvement in the vast majority of patients, and also allowed their normal immunosuppressive therapy to be tapered or discontinued.

Sfikakis *et al*¹² were the first to show the beneficial effect of infliximab on sight-threatening episodes of uveitis in five patients with BD, and a number of similar case reports soon followed.^{13,14,16,17} Further case series, including patients with other types of uveitis, appeared,^{15,18–20} but three recent studies, in particular, require more detailed mention. Sfikakis *et al*²¹ reported on the use of infliximab in 25 patients with BD. In 24 patients, acute ocular inflammation was rapidly controlled starting 1 day after treatment. Complete response of vitritis and retinitis was achieved at day 7 in 68 and 44% of patients, respectively, and in 100% of patients at day 28. Retinal vasculitis resolved in 6% of patients by day 7, 61% of patients by day 14, and 94% of patients by day 28. Cystoid macular oedema resolved in 90% of patients by day 28. Visual acuity improved remarkably in all patients, and no further relapses were observed within the 28 days. Overall, the mean number of relapses ($\pm$ SD) within 32 weeks decreased from 2.5 ± 0.6 before treatment to 0.5 ± 0.7 during infliximab therapy. Concomitant immunosuppressive therapy was substantially reduced. Ohno *et al*²² reported a reduction of the mean number of ocular attacks in patients with BD (converted to frequency per 14 weeks) from 3.96 to 0.98 times, following treatment with infliximab at 5 mg/kg.²⁰ Markomichelakis *et al* have shown infliximab to be effective in uveitis patients with long-standing cystoid macular oedema.²³ Anatomical and functional improvement was noted in eight out of 14 eyes after a single infusion and this was sustained for 6 months. Although relapse was seen in a number of eyes, this improved after a repeat infusion.

In all studies, infliximab has been well tolerated with virtually no major side effects, although two cases of tuberculosis have been reported.^{17,20} To date, there are no reports on the use of adalimumab in uveitis; however,

personal experience in our unit has shown it to be as effective as infliximab in maintaining remission in BD.

Despite small study numbers, there is now enough consistent evidence to suggest that anti-TNF- α therapy, in particular infliximab, has an important role to play in the management of uveitis in BD (a view also held by others²⁴), and perhaps other types of uveitis resistant to more conventional forms of immunotherapy. Repeat infusions may be required to maintain long-term remission.

Unfortunately, the major drawback of anti-TNF- α therapy is the cost; a single infusion of infliximab for a patient weighing 70 kg (5 mg/kg) is about £1580 (British National Formulary). The annual cost per patient (70 kg, 3 mg/kg) for rheumatoid arthritis has been estimated at almost £11 000 per annum (Drugs and Therapeutics Bulletin). We appreciate that there are no randomised controlled trials (RCT) that would be regarded as the gold standard, but until funding is found to undertake a large multicentre trial, we must rely on the best available level of evidence. Yet, very few RCTs exist for conventional immunotherapy for patients with sight-threatening uveitis;²⁵ however that has not prevented the majority of these agents being in common use. We hope that the evidence presented here will be strong enough to influence funding agencies to finance anti-TNF- α therapies for BD and other types of uveitis, as preservation and improvement of vision and quality of life in this group of young adults should be our foremost priority.

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