

## Current Biologic Agents in the Treatment of Uveitis

Melissa C Tien,<sup>1,2</sup> *MBBS, BSc*, Stephen CB Teoh,<sup>1,2</sup> *MMed (Ophth), FRCSEd (Ophth)*

### Abstract

**Introduction:** This review summarises current biologic agents commonly used in the treatment of uveitis. **Methods:** A literature search was conducted using the PubMed interface, looking specifically at randomised controlled studies, retrospective studies and case reports involving the use of biologic agents in the treatment of ocular inflammation. The following key words were used: uveitis, biologic agents, ocular inflammatory disease, pathophysiology and uveitis. In addition, relevant information was also included from selected ophthalmology textbooks. **Results:** A variety of biologic agents are being applied to the treatment of ocular inflammation. Randomised controlled trials addressing the use of such agents are lacking but there exist several case reports and case series studies which show the targeted therapeutic efficacy of various biologic agents tailored to the pathophysiology of ocular inflammatory disease. **Conclusion:** Biologic therapies provide clinicians with new, alternative treatment options for treating sight-threatening refractory uveitis, avoiding the side effects of long-term corticosteroid and steroid-sparing agent use.

Ann Acad Med Singapore 2007;36(Suppl):31-9

**Key words:** Immunosuppression, Ocular inflammatory disease, Steroid-sparing

### Introduction

Uveitis is a general term describing inflammation of one or all parts of the uveal tract. Deleterious effects on vision, either by acute ocular inflammation or by its sequelae, such as cataracts, glaucoma and retinal vascular ischaemia, make uveitis one of the major causes of visual loss.<sup>1</sup> Uveitis can be broadly classified into those associated with infections and uveitis of a non-infectious aetiology, of which association with systemic autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are well recognised.

Traditionally, corticosteroids are the mainstay treatment in immune-mediated uveitis. Although able to provide prompt and highly effective reduction in inflammation, its wide range of significant side effects precludes long-term usage in high doses. Conventional “steroid-sparing agents” such as antimetabolites, alkylating agents and T-cell inhibitors have proven anti-inflammatory effect associated with improvement in clinical symptoms and quality of life.<sup>2</sup> However, these agents too have potentially serious side effects and patients treated with these medications require careful monitoring for electrolyte imbalances, transaminitis and blood dyscrasias.

Scientific research has identified the key role played by

pro-inflammatory chemokines in non-infectious ocular inflammation, such as tumour necrosis factor alpha (TNF- $\alpha$ ), interleukins 1, 2 and 6 (IL-1, IL-2, IL-6) and interferon gamma (IFN- $\gamma$ ).<sup>3</sup> It is against these chemokines and their respective receptors that some biologic agents are designed to act, whilst other biologic agents are designed to counteract the secretors of these chemokines, T- and B-cells, thereby aiming to prevent a downward cascade of inflammation. These agents are not only antibodies and antagonists but are also small molecules that inhibit cellular interactions that modulate inflammatory response. As such, biologic agents are also termed “biologic response modifiers”.

Though not fully studied, biologic agents are a new promising option for patients either unresponsive to, or unable to tolerate conventional immunosuppressive therapies, allowing tapering of medication whilst maintaining disease control and in certain cases, remission. This review aims to highlight the current use of biologic agents commonly used in the treatment of uveitis and other ocular inflammatory conditions.

### Anti-cytokine Therapy

#### *Anti-tumour Necrosis Factor Alpha*

Tumour necrosis factor alpha (TNF- $\alpha$ ), an inflammatory

<sup>1</sup> Department of Ophthalmology, Tan Tock Seng Hospital, Singapore

<sup>2</sup> The Eye Institute, National Healthcare Group, Singapore

Address for Correspondence: Dr Stephen CB Teoh, The Eye Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

Email: Stephen\_Teoh@tsh.com.sg

cytokine produced by macrophages and activated T-cells, plays a key role in neutrophil activation and upregulation of endothelial adhesion molecules. It not only stimulates the proliferation of macrophages, T- and B-cells and T-cell production of pro-inflammatory lymphokines, but is also involved in immunoregulation, host defence, immunosurveillance and cell apoptosis.

The use of anti-TNF agents has revolutionised the treatment of chronic refractory inflammatory disorders. Its efficacy has been proven without doubt in the treatment of systemic diseases such as RA, juvenile idiopathic arthritis (JIA), as well as endogenous, non-infectious refractory uveitis associated with Behcet's disease and sarcoidosis.

In experimental models, TNF- $\alpha$  has been well demonstrated to play a role in the pathogenesis of uveitis. De Vos et al<sup>4</sup> showed a rise in aqueous humour and serum TNF- $\alpha$  levels in endotoxin-induced uveitis (EIU). Likewise, in experimental autoimmune uveoretinitis (EAU), a CD4 T-helper cell mediated autoimmune response, the roles of anti-TNF- $\alpha$  in suppressing inflammation have also been consistently demonstrated.<sup>5</sup> Of the anti-TNF- $\alpha$  agents available, 3 agents have been described in ocular inflammatory conditions – infliximab, adalimumab and etanercept. Infliximab appears to be most promising and most extensively studied.

### Infliximab

Infliximab is a chimeric monoclonal antibody that irreversibly and competitively inhibits both membrane bound and circulating TNF- $\alpha$  rapidly. It is to date the most commonly used biologic agent in the treatment of uveitis and its efficacy has been particularly promising, especially in sight-threatening Behcet's associated uveitis. Successful treatment has also been reported for sarcoidosis, bird-shot chorioretinopathy and multifocal choroiditis (Table 1).

In a prospective trial for the treatment of refractory uveitis, Suhler et al<sup>6</sup> treated 23 patients with infliximab infusions over a period of 50 weeks. Patients received infliximab intravenous (IV) infusions at doses of 3 to 5 mg/kg at weeks 0, 2 and 6 with clinical response being determined at the 10<sup>th</sup> week. Thereafter, patients received an infusion of infliximab at 8-week intervals.

In this study, the authors reported that 18 out of 23 patients (78.3%) responded to therapy at the 10<sup>th</sup> week, with reduced inflammation and improvement in visual acuity. Although generally well tolerated, the authors reported an increased rate of serious adverse events including 3 thrombotic events and 1 new onset of congestive cardiac failure.

In a smaller prospective study, Joseph et al<sup>7</sup> reported therapeutic success in the treatment of 5 patients with posterior uveitis unresponsive to the use of other immuno-

suppressive agents. Three of their patients had posterior uveitis associated with Behcet's disease and 2 had posterior segment intraocular inflammation (PSII). Infliximab infusions were given at a dose of 5 mg/kg at weeks 0, 2 and 6.

At 6 weeks, 4 out of 5 patients responded to therapy with remission of posterior uveitis and improvement in visual acuity. Two of these patients relapsed at months 4 and 5 but remission was achieved in the patient with Behcet's associated uveitis with a repeated dose of infliximab. The other, with idiopathic posterior uveitis, did not respond as well. At 6 months, all 4 patients had successfully withdrawn from other forms of immunosuppressive therapy.

One patient, despite extensive pre-treatment evaluation for tuberculosis, developed pulmonary tuberculosis after receiving infliximab, requiring anti-tuberculous medication.

Despite initial success with infliximab, some patients develop a decreasing response to the drug, possibly due to the development of antibodies to the murine portion of the chimeric molecule. Moreover, side effects can be serious and life threatening, warranting close monitoring of its safety and efficacy in its use for treatment of ocular inflammation. Since the approval of treatment of Crohn's disease and RA with Infliximab by the Food and Drug Administration (FDA) in 1998, there have been rising number of reports of possible lymphomas related to the use of anti-TNF medications.<sup>8</sup> It is imperative that physicians bear the potential development of lymphoproliferative disorders in mind when administering infliximab. With careful monitoring, infliximab is an effective and encouraging treatment option for patients suffering from refractory and sight-threatening uveitis.

### Etanercept

Etanercept is a dimeric soluble form of the extra cellular ligand-binding protein linked p75 TNF receptor. It has the ability to bind to soluble TNF- $\alpha$  and TNF- $\beta$  thereby blocking binding to cell surface TNF receptors. However, the complex interaction is unstable and dissociates rapidly which may then only neutralise TNF- $\alpha$  transiently.

Currently approved by the USA FDA for the treatment of RA and psoriatic arthritis, its use in the treatment of uveitis has been evaluated by a number of small studies. Results have not been spectacular; case reports have documented a worsening of anterior uveitis and the development of scleritis in patients, even though the systemic inflammatory disease was brought under control (Table 2).<sup>9-13</sup>

Reiff et al<sup>14,15</sup> reported success in the use of etanercept for the treatment of refractory uveitis in children, but other small studies have not reported any apparent benefit of etanercept use in the treatment of both adult and childhood uveitis. Galor et al<sup>16</sup> performed a retrospective analysis on

Table 1. Prospective Studies Ocular Inflammatory Disease Treated With Infliximab

Author	n	Types of disease	Response	Dosage	Complications
Suhler et al <sup>4</sup>	23	Idiopathic uveitis, Behcet's disease, sarcoidosis, bird-shot chorioretinopathy, multifocal choroiditis, Crohn's disease, pars planitis unrelated to multiple sclerosis	18 out of 23 patients (78.3%) responded to therapy	3 mg/kg infusions if on concurrent immunosuppressants  5 mg/kg infusions if not on concurrent immunosuppressants  Infusions given at weeks 0, 2 and 6 and 8-weekly thereafter	Myocardial infarction, polyarthritis, new-onset congestive cardiac failure, endometrial carcinoma, non-clearing vitreous haemorrhage, recurrent vitreous haemorrhage, infusion reactions, serum sickness and nephrolithiasis
Joseph et al <sup>5</sup>	5	Behcet's disease, PSII	4 out of 5 (80%) patients responded to therapy at 6 weeks. 2 relapsed remission was achieved with an additional infusion of infliximab	5 mg/kg infusions at 0, 2 and 6 weeks and 8-weekly thereafter	Pulmonary tuberculosis (1 patient)
Niccoli et al <sup>6</sup>	12	Behcet's disease	9 out of 12 patients (75%) achieved complete remission	5 mg/kg over a 12-month period.	Nil serious adverse events reported
Benitez-del-Castillo et al <sup>7</sup>	7	Behcet's disease, sarcoidosis, chronic idiopathic multifocal choroiditis	6 out of 7 patients (85.7%) responded after the first dose. All eyes showed reduced inflammation at 36 months	5 mg/kg infusions at weeks 0, 2 and 6. Repeat infusion administered if patient underwent relapse	Nil ocular or systemic adverse events reported Improvement in subcutaneous granulomas in patient with sarcoidosis

PSII: posterior segment intraocular inflammation

22 patients treated with anti-TNF $\alpha$  therapy, comparing the effectiveness of etanercept versus infliximab in the treatment of ocular inflammation. They reported a statistically significant difference in the reduction of the inflammation recurrence rate, topical steroid use and treatment response in patients treated with infliximab compared to those treated with etanercept. Whilst there was an initial response in patients treated with etanercept, all eventually required a change in medication to control inflammation.

In summary, whilst proven to be useful in the treatment of systemic RA and juvenile chronic arthritis, etanercept's efficacy is still controversial for ocular inflammatory disease.

### Adalimumab

Adalimumab is a fully humanised recombinant anti-TNF- $\alpha$  specific monoclonal IgG1 antibody. Like infliximab, it has the ability to cause sustained neutralisation of membrane bound TNF- $\alpha$ . Administered subcutaneously, the use of adalimumab in the treatment of systemic RA has been shown to be effective but studies to prove its effectiveness in the treatment of ocular inflammatory disorders are largely lacking.

More recently, Biester et al<sup>17</sup> performed a retrospective analysis on 18 patients (children and young adults) treated with adalimumab for refractory juvenile uveitis, both

associated with and without arthritis. Twenty to 40 mg injections were given at 2 weekly intervals and increased to a weekly dose if treatment was deemed ineffective.

Of 18 patients, 16 responded to treatment. One had a mild response and 1 did not respond. Therapeutic response was noted within a period of 2 to 16 weeks after commencement of treatment and 15 children were able to come off systemic steroid treatment completely whilst the other 3 children were able to tolerate a lowered dose of corticosteroids.

In this study, side effects of the injection of adalimumab included a mild localised reaction in 1 child, burning sensations and pain surrounding the injection site. There were no anaphylactoid reactions reported and apart from one patient developing herpes simplex keratitis (HSV)-keratitis, no other severe infections were reported.

In summary, adalimumab could be an alternative immunosuppressive drug for the treatment of uveitis. Its use in the treatment of juvenile uveitis and arthritis could help to avoid the side effects of growth retardation and Cushing syndrome associated with corticosteroid use.

### *Anti-interleukin Therapies*

Interleukins are a family of cytokines that regulate the growth and function of lymphocytes. Interleukin-1 (IL-1) is produced mainly by macrophages and stimulates

Table 2. Studies of Ocular Inflammatory Disease and Inflammatory Joint Disease Treated With Etanercept

Author	n	Types of disease	Response	Dosage	Complications
Smith et al <sup>8</sup>	16	RA, JRA, AS, psoriatic spondyloarthritis, uveitis unassociated with systemic disease	Etanercept – 6 out of 16 (38%) patients achieved reduced ocular inflammation  Infliximab – 2 out of 2 (100%) achieved reduced ocular inflammation  All patients with active joint inflammation responded to therapy with either etanercept or infliximab	14 patient treated with 25 mg of subcutaneous etanercept twice weekly  2 patients received 3 mg/kg infliximab infusions at 0, 2 and 6 weeks and 2 monthly or every 5 weeks thereafter	Etanercept – 1 patient developed new onset scleritis. 2 developed uveitis after initiation of treatment  Infliximab – arthralgia, myalgia and gastrointestinal disturbance
Galor et al <sup>13</sup>	22	HLA-B27 associated uveitis, JIA, RA, Crohn's disease, AS, relapsing polychondritis, sarcoidosis, bird-shot chorioretinopathy, idiopathic uveitis, suspected Cogan's syndrome	Patients treated with infliximab had a statistically significant higher rate of decrease in uveitis (59% vs. 0%, $P = 0.004$ ) compared to those treated with etanercept	Etanercept - Subcutaneous injections at a dose of 25 mg, twice weekly  Infliximab – final dose $7 \pm 1$ mg/kg 8-weekly after commencement of loading doses	2 patients developed uveitis after commencement of etanercept for active joint disease
Reiff et al <sup>11</sup>	10	JRA	10 out of 16 (63%) eyes treated showed decreased inflammation including remission in 4 eyes	Subcutaneous injections of etanercept at a dose of 0.4 mg/kg twice weekly for the first 3 months. Dose increased to 25 mg/kg for at least 3 months if no improvement noted	Mild injection site reactions
Foster et al <sup>12</sup>	20	Idiopathic uveitis, HLA-B27 associated uveitis, SLE, RA, JRA	3 out of 10 patients (30%) treated with etanercept suffered a relapse in uveitis when methotrexate was tapered compared with 50% relapse rate in those not treated with etanercept	Subcutaneous injections of etanercept at a dose of 25 mg, twice weekly	Etanercept treated patients – increased narcolepsy and cataplexy, urinary tract infection, gastrointestinal disturbance, headache

AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; JRA: juvenile rheumatoid arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus

T-helper cells to differentiate and produce other cytokines such as interleukin-2 (IL-2). In turn, IL-2 stimulates both cytotoxic T-cell and T-helper cell growth. Interleukin receptor antagonists specifically prevent T-cell activation and proliferation. With knowledge of the occurrence and properties of naturally occurring interleukin antagonists, such as interleukin 1-RA, biologics designed to mimic the action of such antagonists help provide targeted immunomodulation.<sup>18</sup>

### Daclizumab

Daclizumab is a recombinant humanised immunoglobulin G monoclonal antibody that acts as an IL-2 receptor antagonist. IL-2 receptors are expressed on activated T-cell

surfaces during inflammation, antagonising the receptor and preventing T-cell proliferation and differentiation.

Well-established to prevent organ rejection in patients receiving renal transplants, the use of daclizumab has also been reported to prevent rejections of cardiac and liver transplants.<sup>19-21</sup> In 1999, Nussenblatt et al<sup>22</sup> first described successful long-term treatment with daclizumab in patients suffering from severe bilateral uveitis.

In a more recent retrospective study of 14 patients (27 eyes) with ocular inflammatory disorders refractory or intolerant to conventional immunosuppressive agents, Papaliodis et al<sup>23</sup> administered intravenous (IV) daclizumab (1 mg/kg) over a period of 1 year. Daclizumab was given

Table 3. Studies of Ocular Inflammatory Disease Treated With Interferon Alpha-2 (IFN- $\alpha$ -2)

Author	n	Types of disease	Response	Dosage	Complications
Kotter et al <sup>31</sup>	50	Behcet's disease	92% of patients had a reduction in inflammation after onset of treatment	Subcutaneous injection at a dose of 6 million units given daily	Localised injection site reactions, flu like symptoms, depression, leukopaenia, fibromyalgia, autoimmune phenomena, worsening of seizures, alopecia and worsening of psoriasis
Bodaghi et al <sup>32</sup>	45	Behcet's disease, pars planitis, VKH, idiopathic panuveitis or uveo-papillitis, bird-shot chorioretinopathy, serpiginous choroiditis	82.6% of Behcet's associated uveitis was controlled 59% of uveitis unrelated to Behcet's disease was controlled	Subcutaneous injections of 3 million units given thrice weekly. Accompanying doses of IV methylprednisolone over 3 days followed by oral prednisolone (1 mg/kg)	Major side effects – depression and neutropenia Minor side effects – flu-like symptoms, arthralgias, mild transaminitis, Raynaud's phenomenon, retinal lesions (cotton wool spots, haemorrhages, microaneurysms)

VKH: Vogt-Koyanagi-Harada disease

fortnightly for the first 12 weeks, then every 3 weeks for another 12 weeks and finally every 4 weeks until the 52<sup>nd</sup> week. The diseases included in this study were scleritis, sclerouveitis, ocular-cicatricial pemphigoid (OCP), JIA associated uveitis and idiopathic panuveitis.

Sixteen out of 27 eyes showed improvement in inflammation; 3 out of 27 eyes showed no significant change whilst 8 out of 27 eyes showed worsening in inflammation. No serious adverse reactions were reported. Only 1 patient suffered transient leukopaenia, which required temporary cessation of treatment for 4 weeks until cell counts recovered and treatment was resumed.

Recently, subcutaneous administration of daclizumab has been also been investigated. The study by Nussenblatt and colleagues<sup>24</sup> showed that subcutaneous injections of daclizumab at 2 mg/kg not only allowed greater convenience, but was also well tolerated and allowed concomitant immunosuppressive drug load to be reduced by at least 50% with maintenance of visual acuity.

Daclizumab appears to be relatively well tolerated and may be promising in the treatment of ocular inflammatory disorders that do not respond to conventional methods of treatment.

#### Anakinra

Anakinra is a recombinant human interleukin-1 receptor antagonist (rHuIL1Ra). Preliminary murine studies demonstrated successfully suppression of immune-mediated inflammation with both depressed cellular immune response and cytokine production after the administration of anakinra.<sup>25</sup> It has been reported for use in the treatment of chronic infantile neurological cutaneous articular (CINCA) syndrome.<sup>26</sup> This disease may occur as a result of mutations in the CIAS1 gene, which encodes cryopyrin. Cryopyrin regulates the apoptosis of inflammatory cells; its lack

thereof upregulates levels of IL-1. Anakinra competitively inhibits binding of IL-1 and is more effective in the treatment of CINCA syndrome than corticosteroids.

Teoh et al<sup>25</sup> reported successful treatment of posterior uveitis associated with CINCA syndrome in a 4-year-old boy, which had responded poorly to corticosteroids, methotrexate and etanercept. Subcutaneous anakinra was administered at a dose of 1 mg/kg per day until remission was achieved. Inflammatory remission was achieved within the first year of treatment and his uveitis has subsequently remained quiescent, permitting the withdrawal of oral corticosteroids. No adverse side effects were reported.

#### *Interferon Therapy*

Interferons are cytokines produced in response to viral infections. Synthesised and secreted by monocytes, macrophages, neurons and glial cells, these immunomodulatory substances not only disrupt viral replication, but also prevent tumour growth, act against tolerance inducers of autoimmune disease and have an antiproliferative and apoptotic effect on T-cells. Interferons are classified into type 1 (with alpha and beta subgroups) and type 2 interferons, based on their structure and biologic properties.<sup>27</sup>

#### Interferon- $\alpha$

As a therapeutic agent, interferon-alpha (IFN- $\alpha$ ) has been approved for treatment of hepatitis B and C by limiting viral replication and the Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) showed that patients with an initial clinical episode of demyelination and at least 2 characteristic demyelinating lesions within the brain, treatment with interferon- $\beta$ 1a gave a 50% risk reduction in the development of multiple sclerosis.<sup>28</sup> In inflammatory eye disease,

interferon- $\alpha 2$  (IFN- $\alpha 2$ ) has mainly been used in the treatment of uveitis associated with Behcet's disease (Table 3).<sup>29-30</sup>

A major study by Kotter et al<sup>29</sup> in 2003 already reported a response rate of 92% in 50 patients treated for Behcet's associated uveitis with IFN- $\alpha 2$ . More recently, Bodaghi et al<sup>30</sup> evaluated 45 patients with sight threatening uveitis resistant to different types of immunosuppressants or requiring high-dose corticosteroids. In this study, the authors, recognising the potential severity of relapsing uveitis, approached the study with all patients receiving corticosteroids with the initiation of IFN- $\alpha 2$ . The efficacy of treatment with IFN- $\alpha 2$  was determined by tapering the dosage of corticosteroids until a threshold, beyond which led to a relapse of uveitis, was reached. All other immunomodulating agents were discontinued upon the introduction of IFN- $\alpha 2$ . After 4 weeks of treatment, the authors reported that 19 out of 23 patients with Behcet's associated uveitis responded to IFN- $\alpha 2$  therapy whilst 13 out of 22 patients with uveitis unrelated to Behcet's disease showed improvement after commencement on IFN- $\alpha 2$ .

Major side effects of IFN- $\alpha 2$  therapy were seen in 2 patients. One suffered severe depression, leading to permanent cessation of therapy. The other developed significant neutropenia, requiring temporary interruption in treatment. Minor side effects include flu-like symptoms, coughing, Raynaud's phenomenon, arthralgias, mild transaminitis and mild/moderate changes in blood cell counts. Patients suffering from these effects did not require discontinuation of IFN- $\alpha 2$  therapy. Common, but rarely symptomatic ophthalmic side effects include retinal lesions such as cotton wool spots, haemorrhages and micro-aneurysms.

In summary, there is increasing evidence that interferons have a role in the treatment ocular disease, especially in Behcet's associated uveitis for which, it may be used as second-line therapy for refractory disease. Studies are still required to determine the drug dosage and optimum duration of treatment.

## Anti-Lymphocytic Therapy

### *Anti-B Cell Therapy*

#### Rituximab

Rituximab is a recombinant chimeric monoclonal antibody that targets CD-20, a cell surface antigen on B-cells, resulting in B-cell depletion. Initially developed for the treatment of B-cell lymphomas, its use has recently been applied to the systemic treatment of RA, SLE and Wegeners' granulomatosis (WG). With the established role of B-cells in T-cell mediated and immune complex-mediated diseases, this biologic is potentially useful in targeting the effector

cells of the inflammatory cascade.

To date, there have been no randomised control trials (RCT) to show the effectiveness of rituximab for the treatment of ocular inflammation. However, there have been case reports that show therapeutic success in the treatment of scleritis.<sup>31,32</sup> It is postulated that since RA, SLE and WG are conditions associated with scleritis, rituximab could emerge as a promising therapeutic agent for ocular inflammation in these situations.

However, there are more reports on the use of rituximab in the treatment of systemic disease. Smith et al<sup>33</sup> reported disease control in 11 patients with refractory SLE after commencing treatment on rituximab. Whilst the recurrence rate was high, re-treatment with rituximab was effective and also allowed patients to be maintained on a lower dose of oral corticosteroids. Kramm et al<sup>34</sup> treated 5 patients suffering from disease-modifying anti-rheumatic drug (DMARD)-refractory RA with 4 weekly doses of rituximab and achieved remission in 80% after failure of response to anti-TNF therapy.

There have been recent reports of hepatic failure in patients who were hepatitis B carriers, bowel obstruction and perforation, and progressive multifocal leukoencephalopathy (PML) suspected to be associated with the use of rituximab.<sup>35-37</sup> Whilst causative effect has not been directly established, it is suggested that its immunosuppressant effects may be associated with PML.

## Other Biologic Agents

There are other biologic agents being used for the treatment of lymphocytic malignancies and rheumatic disease, such as Campath-1H (alemtuzumab) and newer agents including anti-interleukin-6 antibodies (anti-IL6), and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) therapy. The use of these agents in the treatment of ocular inflammatory conditions is still being explored.

### Campath-1H (Alemtuzumab)

Campath-1H is a humanised monoclonal antibody that acts against the pan-lymphocyte antigen CD52. Currently approved for use in the treatment of chronic lymphocytic leukaemia, campath-1H is also being investigated for the treatment of T-cell mediated disease such as multiple sclerosis and transplant rejection phenomena.<sup>38,39</sup> In 1995, Isaacs et al<sup>40</sup> reported its use in the treatment of 1 patient with refractory non-infectious uveitis, with resultant improvement in visual acuity and inflammation. In 2000, Dick et al<sup>41</sup> described the treatment of 10 patients with severe refractory non-infectious uveitis, intraocular and orbital inflammatory disease and recurrent corneal allograft rejection with campath-1H. Campath-1H was given by intravenous infusion at 10 to 12 mg daily for 5 days and all

patients demonstrated good clinical response. However, the administration of campath-1H was associated with considerable haemotoxicity and there was a demonstrated universal decrease in total peripheral blood lymphocyte numbers during treatment and a protracted decrease in CD4 counts. As such, campath-1H is less widely used now for the treatment of ocular inflammation as more targeted therapies are available.

### Immunoglobulins

Intravenous immunoglobulins are purified immunoglobulin G (IgG) products made from pooled human plasma. As an immunomodulating agent, its therapeutic effect has been reported in the treatment of systemic immune-mediated disease such as Guillain-Barre syndrome and Kawasaki disease, prompting evaluation of its application to the treatment of uveitis.<sup>42,43</sup> In 1999, Rosenbaum et al<sup>44</sup> reported sustained and substantial benefit for 5 out of 10 patients treated with intravenous immunoglobulins for refractory uveitis. Reported side effects included thrombophlebitis, allergic reactions and most significantly, myocardial infarction. Karmochkine et al<sup>45</sup> also reported successful tapering of corticosteroid dose with improved visual acuity and inflammation in patients treated with intravenous immunoglobulins for birdshot chorioretinopathy. Most recently, Seider et al<sup>46</sup> described successful treatment of 4 patients suffering from resistant ocular Behcet's disease with intravenous immunoglobulins. No adverse reactions were reported in this study.

Immunoglobulin therapy is advantageous in that it does not cause immunosuppression and expose the patient to risk of opportunistic infections. However, it is of limited availability, expensive and together with its reported side effects, is not used widely for the treatment of intraocular inflammation.

### Anti-interleukin-6 Therapy

Still in an experimental stage, scientists have been investigating the possible strategy of targeting interleukin-6 (IL-6) in the treatment of uveitis. Ohta et al<sup>47</sup> demonstrated in their study, an upregulation of this pro-inflammatory cytokine within aqueous humour in mice with EIU. They also demonstrated a suppression in T-cell activation when the mice were administered anti-IL-6 antibodies, implying future possibilities of directing targeted treatment against IL-6 for the treatment of uveitis.

### Anti-cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4) Therapy

T-cell co-stimulating molecules are cell surface proteins that play a role in T-cell activation. CTLA-4 is a T-cell surface receptor that has a high affinity for the B7 surface antigen on B-cells and this receptor-ligand interaction is

essential for the induction of T-cells to proliferate and release cytokines.

CTLA-4Fc is a recombinant fusion protein that blocks the interaction between the B-cell surface molecule, B7, and CTLA therefore preventing the activation of T-cells and subsequent pro-inflammatory action. Anti-CTLA-4 antibodies have not been reported for use in the treatment of uveitis but have been applied to the treatment of patients with metastatic melanoma with objective tumour responses.<sup>48</sup>

In animal models of EAU, Verwaerde et al<sup>49</sup> showed that the rodents given intravitreal injections of retinal Müller glial cells transfected with adenovirus expressing CTLA-4-Ig had a strongly protective effects against EAU. Also using the same animal model, Shao et al<sup>50</sup> demonstrated the expression of B7 in the eye at different times during EAU and the inhibition of EAU in rats treated with anti-B7 antibodies. There is also a suggestion that CTLA-4 may represent a candidate gene for disease susceptibility in Fuchs heterochromic cyclitis.<sup>51</sup> Such evidence suggests an attractive alternative in inhibiting antigen presentation for the treatment of immune-mediated disease and further research is necessary to evaluate the role of CTLA-4 antibodies in the treatment of ocular inflammatory disease.

### **Conclusion**

Refractory uveitis along with other treatment-resistant ocular inflammatory disorders can be difficult to treat. Very often, treatment requires prolonged immunosuppression and treatment with corticosteroids and steroid sparing agents have considerable side effects with long-term use.

Studies into the potential use of biologic agents provide ophthalmologists with exciting prospects in successful treatment of such recalcitrant diseases. Infliximab is the most commonly used biologic agent with greatest experience. Moreover, there now exists a larger array of biologic agents that ophthalmologists and physicians can select from, to provide more targeted treatment tailored to the primary driving cytokine response or inflammatory drive. However, there remains a need to for larger long-term randomised controlled studies aimed at investigating the use of these agents, to address the dose, duration efficacy and long-term complications resulting from prolonged biologic agent administration in patients with uveitis.

Treatment benefit must also be balanced against the potential financial implications for both patients and respective health systems. In our local setting, biologics are expensive. On average, infliximab currently costs approximately \$3000 per dose, rituximab and etanercept approximately \$3000 to \$4000 per month of treatment

whilst IFN- $\alpha$ 2 costs approximately \$1200 per month of treatment. Furthermore, biologic agents are not currently subsidised or funded by health insurance, which implicates further financial burden on the patient. With escalating healthcare costs and potential side effects, most importantly those of malignancies, these drugs therefore need to be used judiciously, with the patient being well informed of implications, risks and benefits of therapy.

REFERENCES

1. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol* 1996;80:844-8.
2. Lim L, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. *Clin Experiment Ophthalmol* 2006;34:365-74.
3. Ooi K, Galatowicz G, Calder VL, Lightman SL. Cytokines and chemokines in uveitis – is there a correlation with clinical phenotype? *Clin Med Res* 2006;4:294-309.
4. de Vos AF, van Haren MAC, Verhagen C, Hoekzema R, Kijlstra A. Kinetics of intraocular tumour necrosis factor and interleukin 6 in endotoxin induced uveitis in a rat. *Invest Ophthalmol Vis Sci* 1994;35:1100-6.
5. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). *Prog Retin Eye Res* 2004;23:617-37.
6. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Juiz DE, Pickard TD, et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol* 2005; 123:903-12.
7. Joseph A, Raj D, Dua HS, Powell PT, Lanyon PC, Powell RJ. Infliximab in the treatment of refractory posterior uveitis. *Ophthalmology* 2003;110:1449-53.
8. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development. *Arthritis Rheum* 2002;46:3151-8
9. Niccoli L, Nannini C, Benucci M, Chindano D, Cassara E, Salvarani C, et al. Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. *Rheumatology* 2007 May 3 [Epub ahead of print].
10. Benitez-del-Castillo JM, Martinez-de-la-Casa JM, Pato-Cour E, Mendez-Fernandez R, Lopez-Abad C, Matilla M, et al. Long term treatment of refractory posterior uveitis with anti-TNF alpha (infliximab). *Eye* 2005;19:841-5.
11. Smith JR, Levinson RD, Holland GN, Jabs DA, Robinson MR, Whitcup SM, et al. Differential efficacy of tumour necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum* 2001;45:252-7.
12. Rosenbaum JT. Effect of etanercept on iritis in patients with ankylosing spondylitis. *Arthritis Rheum* 2004;50:3736-7.
13. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology* 2005;44:1008-11.
14. Reiff A, Takei S, Sadeghi S, Stout A, Shaham B, Bernstein B, et al. Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum* 2001;44:1411-5.
15. Foster S, Tufail F, Waheed NK, Chu D, Miserocchi E, Baltatzis S, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol* 2003;121:437-40.
16. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology* 2006;113:2317-23.
17. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;9:319-24.
18. Lim WK, Fujimoto C, Ursea R, Mahesh SP, Silver P, Chan CC, et al. Suppression of immune-mediated ocular inflammation in mice by interleukin 1 receptor antagonist administration. *Arch Ophthalmol* 2005;123:957-63.
19. Beniaminovitz A, Itescu S, Lietz K, Donovan M, Burke EM, Groff BD, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; 342:613-9.
20. Emre S, Gondolesi G, Polat K, Ben-Haim M, Artis T, Fishbein TM, et al. Use of daclizumab as initial immunosuppression in liver transplant recipients with impaired renal function. *Liver Transpl* 2001;7:220-5.
21. Buhaescu I, Segall L, Goldsmith D, Covic A. New immunosuppressive therapies in renal transplantation: monoclonal antibodies. *J Nephrol* 2005;18:529-36.
22. Nussenblatt RB, Fortin E, Schiffman R, Rizzo L, Smith J, Veldhuisen PV, et al. Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase I/II clinical trial. *Proc Natl Acad Sci U S A* 1999;96:7462-6
23. Papaliodis G, Chu D, Foster S. Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003;110:786-9.
24. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, et al. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. *Ophthalmology* 2005;112:764-70.
25. Teoh SC, Sharma S, Hogan A, Lee R, Ramanan AV, Dick AD. Tailoring biological treatment: anakinra treatment of posterior uveitis associated with CINCA syndrome. *Br J Ophthalmol* 2007;91:263-7.
26. Granel B, Serratece J, Disdier P, Weiller PJ. Dramatic improvement with anakinra in a case of chronic infantile neurological cutaneous and articular (CINCA) syndrome. *Rheumatology (Oxford)* 2005;44: 689-90.
27. Mackensen F, Max R, Becker MD. Interferon therapy for ocular disease. *Curr Opin Ophthalmol* 2006;17:567-73.
28. Galetta SL. The controlled high risk avonex multiple sclerosis trial (CHAMPS Study). *J Neuroophthalmol* 2001;21:292-5.
29. Kotter I, Zierhut M, Eckstein AK, Vonthein R, Ness T, Gunaydin I, et al. Human recombinant interferon alpha-2a for the treatment of Behcet's disease with sight threatening posterior or panuveitis. *Br J Ophthalmol* 2003;87:423-31.
30. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong du LT, et al. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. *Br J Ophthalmol* 2007;91:335-9.
31. Cheung CM, Murray PI, Savage W. Successful treatment of Wegener's Granulomatosis associated scleritis with rituximab. *Br J Ophthalmol* 2005;89:1542.
32. Ahmadi-Simab K, Lamprecht P, Nolle B, Ai M, Gross WL. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. *Ann Rheum Dis* 2005;64:1087-8.
33. Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. *Arthritis Rheum* 2006;54:2970-82.
34. Kramm H, Hansen KE, Gowing E, Bridges A. Successful therapy of rheumatoid arthritis with rituximab: renewed interest in the role of B cells in the pathogenesis of rheumatoid arthritis. *Clin Rheum* 2004;10: 28-32.
35. New Safety Issues associated with Rituximab. *Adverse Drug Reaction News March* 2007;Vol 9(1):3.
36. Health Canada Advisory for Healthcare Professionals. Available at: [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/rituxan\\_3\\_hpc-cps\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/rituxan_3_hpc-cps_e.html). Accessed 10 November 2006.

37. US FDA information for Healthcare Professionals. Available at: [www.fda.gov/cder/drug/infopage/rituximab/default.htm](http://www.fda.gov/cder/drug/infopage/rituximab/default.htm). Accessed 18 December 2006.
38. Alinari L, Lapalombella R, Andritsos L, Baiocchi RA, Lin TS, Byrd JC. Alemtuzumab (Campath-1H) in the treatment of chronic lymphocytic leukemia. *Oncogene* 2007;26:3644-53.
39. Cree B. Emerging monoclonal antibody therapies for multiple sclerosis. *Neurologist* 2006;12:171-8.
40. Isaacs JD, Hale G, Waldmann H, Dick AD, Haynes R, Forrester JV, et al. Monoclonal antibody therapy of chronic intraocular inflammation using Campath-1H. *Br J Ophthalmol* 1995;79:1054-5.
41. Dick AD, Meyer P, James T, Forrester JV, Hale G, Waldmann H, et al. Campath-1H therapy in refractory ocular inflammatory disease. *Br J Ophthalmol* 2000;84:107-9.
42. Gedalia A. Kawasaki disease: 40 years after the original report. *Curr Rheumatol Rep* 2007;9:336-41.
43. Gürcan HM, Ahmed AR. Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders. *Ann Pharmacother* 2007 41:812-23.
44. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. *Am J Ophthalmol* 1999;127:545-9.
45. Karmochkine M, Kazatchkine M, Lehoang P. Intravenous immunoglobulin in autoimmune uveitis. *Ann Intern Med* 1998;129:1078-9.
46. Seider N, Beiran I, Scharf J, Miller B. Intravenous immunoglobulin therapy for resistant ocular Behcet's disease. *Br J Ophthalmol* 2001;85:1287-8.
47. Ohta K, Yamagami S, Taylor AW, Strelein JW. IL-6 antagonises TGF- $\beta$  and abolishes immune privilege in eyes with endotoxin-induced uveitis. *Invest Ophthalmol Vis Sci* 2000;41:2591-9.
48. Maker AV, Phan GQ, Attia P, Yang JC, Sherry RM, Topalian SL, et al. Tumour regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin: a phase I/II study. *Ann Surg Oncol* 2005;12:1005-16.
49. Verwaerde C, Naud MC, Delanoye A, Wood M, Thillaye-Goldenberg B, Auriault C, et al. Ocular transfer of retinal glial cells transduced ex vivo with adenovirus expressing viral IL-10 or CTLA-Ig inhibits experimental autoimmune uveoretinitis. *Gene Ther* 2003;10:1970-81.
50. Shao H, Sun D, Sun SL, Cruze JM, Bora N, Kaplan HJ. Expression of B7 molecules in the eye during experimental autoimmune anterior uveitis (EAAU). *Curr Eye Res* 2002;25:271-7.
51. Spriewald BM, Lefter C, Huber I, Lauer B, Wenkel H. A suggestive association of fuchs heterochromic cyclitis with cytotoxic T cell antigen 4 gene polymorphism. *Ophthalmic Res* 2007;39:116-20.