The treatment of non-infectious uveitis is a challenge to clinicians. The treatment involves suppressing the deleterious effects of inflammation caused by the patient's own immune system. Corticosteroids are the mainstay of treatment for non-infectious uveitis. They have several advantages. They are rapidly effective, inexpensive, potent and work in almost all types of non-infectious uveitis. Their side effects prevent the use of corticosteroids in high doses for long-term control of inflammation. Conventional “steroid-sparing agents” such as antimetabolites, alkylating agents and T-cell inhibitors have helped reduce the need for corticosteroids and improved quality of life. They have the risk of serious, life threatening adverse effects and may be of limited efficacy in some cases. Biologic therapy can be an alternative in patients who are refractory to treatment or who are intolerant of conventional immunotherapy.

What are biologics?

Several pro-inflammatory chemokines play a key role in non-infectious ocular inflammation, such as tumour necrosis factor alpha (TNF-α), interleukins 1, 2 and 6 (IL-1, IL-2, IL-6) and interferon gamma (IFN-γ). Some biologic agents or “biologic response modifiers” act against these chemokines and their respective receptors. Others are designed to counteract the secretors of these chemokines, T- and B-cells.

Naming of biologic agents

Monoclonal antibodies (mAb), when used as medications, are given a generic name ending in “-mab” An antecedent “u”(-umab) indicates a human antibody; “xi”(-ximab) indicates a mixed human-murine (chimeric) antibody. Fusion proteins, which typically contain either receptor domains or cell surface markers, are given a generic name ending in “-cept.”

How effective are biologics?

Biologics are relatively new medications, and data on both efficacy and safety of these agents used to treat ocular conditions are limited. They were initially developed to treat systemic inflammatory diseases. Ocular inflammation can occur with many of these diseases and small uncontrolled case...
series have appeared in the literature regarding the control of the ocular inflammation in these patients. Most of the literature describing biologic treatment of uveitis is with the tumor necrosis factor inhibitors (infliximab, etanercept and adalimumab), followed by the IL-2 receptor (IL2-R) blocker daclizumab. Many of these studies were complicated by the fact that most patients with uveitis have been treated with more than 1 immunosuppressive agent, making it hard to determine the adverse effects of individual drugs. Some of the recent literature on biologics will be discussed in the following section.

ANTI CYTOKINE THERAPIES

Tumour necrosis factor alpha (TNF-α), an inflammatory cytokine produced by macrophages and activated T-cells. It stimulates the proliferation of macrophages, T- and B-cells and T-cell production of pro-inflammatory lymphokines, upregulation of endothelial adhesion molecules and is also involved in immunoregulation, host defence, immunosurveillance and cell apoptosis.

Infliximab

Infliximab is a chimeric monoclonal antibody that irreversibly and competitively inhibits both circulating and membrane-bound TNF-α. Infliximab has been reported to be effective in the treatment of Behcet’s panuveitis, posterior uveitis, juvenile idiopathic arthritis (JIA) associated uveitis and retinal vasculitis1-3. 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. Suhler and Smith et al recently reported their results with the use of infliximab in a recent prospective study with at least 2 years of follow-up4. It was effective in selected patients, with 60% of patients retained in the study per year. Their 1-year data, published in 2005 reported reasonable initial success, but an unexpectedly high incidence of adverse events2. Of their 23 patients, 7 developed serious adverse events, including 3 thromboses, 1 malignancy, 1 new onset of congestive heart failure, and 2 cases of drug-induced lupus. 75% of their patients, who received at least 3 injections of infliximab, also developed elevated antinuclear antibody titers. Of 23 patients who demonstrated initial success at 10 weeks, 15 completed 1 year in the study and 8 completed 2 years of therapy. Three patients developed a drug-related lupus-like illness. Two developed fatal solid malignancies. Some of the adverse events in this series, drug induced lupus, for example, are more frequent than reported in the rheumatologic literature. In an accompanying editorial Goldstein expresses the opinion that patients with isolated uveitis may be different from those with systemic disease5. It may be that patients with systemic inflammatory disease have TNF levels that are higher than in patients with localized inflammation such as uveitis. In rheumatoid arthritis, infliximab might therefore reduce TNF to a normal level, while in uveitis infliximab might result in an inappropriately low level of serum TNF. If this is true, uveitis associated with systemic diseases such as Behcet disease and sarcoidosis might be safer to treat with infliximab than idiopathic disease confined to the eye.

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-α and TNF-β thereby blocking binding to cell surface TNF receptors. However, this interaction is unstable and dissociates rapidly which may then only neutralise TNF-α transiently. Results have not been encouraging. There have been case reports of worsening of anterior uveitis and the development of scleritis in patients, even when the systemic inflammatory disease was under control6. One study reported that etanercept was not superior to placebo in preventing relapses of uveitis in previously controlled patients attempting
to taper methotrexate. Therefore while etanercept has shown efficacy in the treatment of systemic RA and JIA, is still controversial for ocular inflammatory disease.

**Adalimumab**

Adalimumab is a fully human monoclonal antibody against TNF-α. It is delivered by subcutaneous injections. A retrospective study for JIA uveitis revealed that adalimumab effectively controlled inflammation in approximately one-third of patients refractory to previous treatment with infliximab or etanercept. A prospective study of adalimumab in 19 adults with various uveitis reported control of inflammation in 63 percent of patients and complete resolution of CME in 55 percent of eyes at one year of therapy. One study showed that adalimumab could be an effective alternative for treatment of Behcets Disease-associated panuveitis in patients already well-controlled with infliximab.

**ANTI INTERLEUKIN THERAPIES**

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

**Daclizumab**

Daclizumab is a recombinant humanised immunoglobulin G monoclonal antibody that binds to the IL-2 receptors on activated T cells preventing their IL2-dependent activation. A study of intravenous daclizumab for the treatment of non-infectious uveitis demonstrated improvement of inflammation and visual acuity at one year in eight of 10 patients, which was maintained after four years of treatment. When the infusions were reduced to six-weekly intervals from the initial four-weekly infusions increased uveitic recurrences were observed. After four years of intravenous infusions, some patients were could be switched to maintenance subcutaneous daclizumab therapy with good response. Ten of 15 patients in a subsequent study by Nussenblatt et al achieved at least a 50-percent reduction of concurrent immunosuppression with retained visual acuity, inflammatory control, and no significant side effects. However, daclizumab failed to demonstrate effectiveness in Behcets Disease-associated uveitis in a randomized trial.

**INTERFERON THERAPY**

Interferons (IFN) are cytokines produced in response to viral infections. These immunomodulatory substances disrupt viral replication, 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.

**Interferon-α**

Interferons have been reported to be useful in the treatment of refractory ocular inflammation and associated macular edema, particularly in patients with Behcets Disease and multiple sclerosis. However, relapse is frequently seen after discontinuation of therapy, and potentially serious complications may occur. Multiple cases of possible IFN-induced sarcoidosis with or without uveitis have been reported.

**Other biologics**

Other biologics under current study include efalizumab, rituximab, the IL-1 blocker anakinra and the T-cell costimulation inhibitor abatacept. Efalizumab blocks the pan-leukocyte surface marker CD11a and is under current study for non-infectious uveitis with macular edema. The B-cell antagonist...
rituximab is currently under study for treatment of scleritis and orbital inflammation.

Vascular endothelial growth factor inhibitors, including bevacizumab and ranibizumab, widely

used to treat age-related macular degeneration and other retinal vascular diseases, have reported benefit in reducing uveitic CME in selected patients with otherwise well-controlled uveitis, at least transiently.

### DOSAGE AND ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>NAME</th>
<th>ROUTE</th>
<th>DOSE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI CYTOKINE THERAPIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFliximab</td>
<td>IV</td>
<td>Loading: 3-5 mg/kg at weeks 0, 2 and 6. Maintenance: 3-6 mg/kg every 4-8 weeks, max dose 20 mg/kg body weight in children</td>
<td>Susceptibility to infections including reactivation of tuberculosis, hepatitis B, histoplasmosis. Demyelinating disease, lupus like syndrome, malignancy, thromboembolism, cardiac failure, Hypersensitivity reactions.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>SC</td>
<td>40 mg every 1-2 weeks (&lt;30 kg, 20 mg every 2 weeks)</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>SC</td>
<td>Adults: 25 mg twice weekly or 50 mg once weekly. Children 0.8 mg/kg/week (max 50 mg/wk)</td>
<td></td>
</tr>
<tr>
<td><strong>ANTI INTERLEUKIN THERAPIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>IV, SC</td>
<td>1-2 mg/kg every 2-4 weeks</td>
<td>Hypersensitivity reactions, Headache, GI upset.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>500 or 1000 mg at week 0 and week 2.</td>
<td>Infusion reactions, nausea, hypertension. Progressive multifocal leukoencephalopathy, severe mucocutaneous reactions.</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td>SC</td>
<td>3-6 IU/day, taper over 6 months.</td>
<td>Flu like symptoms, bone marrow suppression, local injection site reactions</td>
</tr>
<tr>
<td>Intravenous Immunoglobulin</td>
<td>IV</td>
<td>0.4 gm/kg for five days/month or 0.5 gm/kg 3 days/month.</td>
<td>Thrombotic events, Blood borne infection transmission</td>
</tr>
</tbody>
</table>
Intravenous immunoglobulins are purified immunoglobulin G (IgG) products made from pooled human plasma. Intravenous immunoglobulin (IVIg) has been used successfully for treatment of refractory uveitis. IVIg is not associated with systemic immunosuppression, reducing the risk of opportunistic infection. However, IVIg is extremely expensive and can cause severe side effects including thromboembolism, aseptic meningitis and bloodborne infections, and is usually reserved as a treatment of last resort.

**Precautions in the use of Biologics**

**Tuberculosis**

Biologics have been known to reactivate latent tuberculosis (TB). They should be avoided in patients with a past history of TB or in any infectious uveitis. Use with caution if tuberculin test positive. If absolutely required a cover of anti tuberculous drugs can be provided.

**Second immunosuppressive agents**

A second immunosuppressive agent should be administered along with infliximab and also with etanaercept and adalimumab. Methotrexate is usually the drug of choice. It improves long term disease control and reduces the relapse rate. Since development of antibodies to the drug is common the methotrexate additionally suppresses this as well as suppressing hypersensitivity reactions.

**Malignancy**

Increased risk of solid tumours. Avoid TNF inhibitors in those with history of malignancy or treatment with history of previous use of alkylating agents.

**Demyelinating disease**

TNF inhibitors may cause or worsen demyelinating disease. Use with caution in patients with intermediate uveitis with neurological symptoms or family history of demyelinating disease. Avoid in persons with history of multiple sclerosis.

**Vaccines**

Avoid administering live vaccines concurrently and for three months after stopping medications. If there is significant exposure to the varicella virus discontinue the drug and administer varicella zoster immunoglobulin.

**Monitoring blood parameters**

**Infliximab and Daclizumab**: Monitor complete blood counts and biochemical parameters for all infusions. Monitor anti nuclear antibody additionally for infliximab.

**Adalimumab**: complete blood work up at start of therapy and whenever additional doses are given, routine monitoring 6 monthly. Most biologics are given with a second immunosuppressive agent so blood tests need to be ordered as per the protocol for the second agent.

**Use in Pregnancy and Lactation**

In general, biologics should not be used in pregnant or lactating women unless the potential benefit justifies the risk to the fetus/infant. This is not substantiated by long term study. Thorough discussion with the patient of the risks and benefits, both ocular and obstetric, is required, and consultation with an obstetrician experienced in high-risk pregnancies is invaluable in these situations.

In conclusion, biologics are potent new agents that may help in control of certain forms of uveitis that are refractory to more traditional immunosuppressive therapies. The types of uveitis most likely to benefit are those associated with systemic inflammatory conditions such as Behcet’s disease and JIA. Side effects are both serious and relatively common. Patients should be apprised of both the risks as well as the potential benefits of these agents. Their use in India may be limited due to the risk of reactivation of latent tuberculosis and because of the prohibitive cost and limited long-term safety data. Their use should be monitored by experienced uveitis specialists and rheumatologists.

**References**


