Advances in the Treatment of Noninfectious Uveitis with Biologics: Anti-TNF and Beyond

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Chapter: Tumor Necrosis Factor Alpha (TNF-α) Antagonists

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Introduction

Tumor necrosis factor alpha (TNF-α) is a pleiotropic cytokine expressed in a wide variety of inflammatory conditions contributing to the pathogenesis and perpetuation of autoimmune diseases. It is produced by different cell types and mediates its effects through two receptors, p55 (TNFR1) and p75 (TNFR2) [1]. During inflammation TNF-α activates T cells and macrophages and up regulates other proinflammatory cytokines. Experimental models of uveitis have provided substantial evidence of TNF-α’s pivotal role in mediating intraocular inflammation [2,3]. Several studies showed that the serum and/or aqueous humor concentrations of TNF-α and soluble TNF-α receptors are increased in non-infectious uveitis, especially during periods of higher disease activity [4-7]. In late 1990s Dick et al. demonstrated the benefits of TNF-α inhibition in minimising the severity of experimental autoimmune uveoretinitis [8]. Neutralizing TNF-α activity results in skewed T-cell polarization with reduced IFNγ generation, suppressed levels of T-cell apoptosis, and reduced levels of classical myeloid cell activation, resulting in suppressing target organ damage [2,8]. There are currently 5 TNF antagonists approved in rheumatic diseases as shown in Table 1. Two broad strategies are used in targeting TNF: soluble receptors (i.e., etanercept) vs targeting antibodies (infliximab, adalimumab, golimumab, certolizumab). Amongst the targeting antibodies, a distinction can be made based on the route of administration (intravenous vs subcutaneous injection) and the level of humanization of the antibody structure (chimeric, humanized, or fully human). TNF inhibitors are the form of biologic therapy most commonly employed to treat uveitis. Although there is increasing evidence of their beneficial effects in the treatment of autoimmune uveitis, TNF inhibitors are not approved for such an indication, and therefore its use is off-label worldwide excepting infliximab for Behçet’s uveoretinitis in Japan.

Etanercept

Etanercept (Enbrel®, Amgen Inc, CA, USA and Wyeth, NJ, USA) is a dimeric protein composed of soluble TNFR and a human IgGFc fragment. It competitively inhibits the binding of TNF-α and TNF-β, thereby resulting in decreased expression of adhesion molecules responsible for leukocyte migration and reduced synthesis of proinflammatory cytokines [9]. It is administered subcutaneously at a dose of 25 mg twice a week or 50 mg once a week. Etanercept has been effective in the treatment of several rheumatic diseases [10,11] although its effect in uveitis is debatable [11-16]. Foster et al. showed that etanercept has no significant efficacy over placebo in preventing relapses of uveitis [11]. Moreover, etanercept can worsen uveitis course or even induce ocular inflammation in a paradoxical effect [13-16].

Infliximab

Infliximab (Remicade®, Centocor, PA, USA) is a chimeric monoclonal antibody whose mechanism of action consists of neutralizing membrane-bound TNF-α and soluble TNF-α and suppressing TNF-α production by macrophages and lymphocytes [17]. An alternative inhibition mechanism of infliximab is the promotion of regulatory T (Treg) cells that acquire suppressive functions in the periphery [18]. Infliximab is the only chimeric TNF-α antagonist, composed of a mouse antigen binding (Fab) domain and a human Fc domain. This is the only TNF inhibitor that is given intravenously. The most frequent dosage regimen is an induction dose of 5 mg/kg at 0, 2, 6, and every 8 weeks thereafter depending on the clinical response. It is approved for use in rheumatoid arthritis, ankylosing spondilitis, psoriatic arthritis and plaque psoriasis and commonly used in Crohn’s disease.

Infliximab has the largest amount of data amongst the different TNF antagonists with respect to treating ocular inflammatory disease. Infliximab has been effective for a variety of forms of uveitis (Juvenile Idiopathic Arthritis (JIA)-associated uveitis, sarcoidosis, Birdshot, diffuse subretinal fibrosis, sympathetic ophthalmia) [19-24], but most of the evidence of the effectiveness of infliximab in ocular inflammatory disease comes from studies on its use in Behçet’s disease [25-31]. Two prospective studies of infliximab for refractory Behçet’s uveitis showed a significant decrease in the mean number of ocular attacks compared with conventional immunosuppressive therapy [25,26]. Recently, Japanese investigators have conducted a multicenter prospective study [28] that shows the efficacy of infliximab in 63 patients with refractory Behçet’s uveitis during the first year of treatment. At 12 months follow-up, uveitis improved in 92% of patients, unchanged in 8%, and worsened in none. An important advantage of infliximab therapy is the rapid onset of action compared with other medications, causing a rapid induction of remission. Control of ocular inflammation is frequently observed within 1 or 2 infusions, and its efficacy seems superior to intravenous methylprednisolone [31]. Rapid and successful management of acute fundus inflammation in ocular Behçet’s disease is imperative to avoid vision loss due to permanent lesions in the retina and optic nerve. The long-term effects of repetitive infliximab infusions in preventing ocular relapses have been evaluated in several open prospective studies. Long-term remission can be sustained after cessation of therapy [29,32,33]. Infliximab is also efficacious in extracocular manifestations of Behçet’s disease such as oral and genital ulcers and/or arthritis in the majority of patients (Figure 1). Recent reports have suggested the possibility of intravitreal use of infliximab [34,35]. Markomichelakis et al. conducted a pilot study in which a single intravitreal injection of infliximab (1 mg/0.05 mL) was given to 15 patients with Behçet’s
uveitis at the onset of a unilateral attack. A statistically significant improvement in visual acuity was observed as well as resolution of intraocular inflammation signs. The authors suggest that intravitreal infliximab may be considered when systemic administration is not feasible or contraindicated. Further studies to assess the efficacy of intravitreal infliximab are required.

Regarding to safety issues, infliximab is considered to be a drug with low toxicity, although allergic reactions are frequent during infusion and usually treated without consequences with antihistamines and analgesics. Its combination with methotrexate is convenient in order to reduce the production of anti-infliximab antibodies associated to multiple infusions. On the other hand, it has to be taken into account that infliximab, like all other TNF antagonists, can reactivate latent tuberculosis (TB) and other opportunistic infections, and thus patients should have their risk of TB assessed with a prior history of exposure, chest X-ray and QuantiFERON assays, given that tuberculin skin test can be altered by the use of steroids and immunosuppressive medications. In addition, the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study showed that patients on anti-TNF therapies have a greater risk of cancer and overall mortality [36]. However, it has been proposed that TNF antagonists do not actually initiate cancer, but exacerbate pre-existing cases of undetected cancer. This statement must be considered when initiating therapy with these agents [37].

The remaining targeting antibodies are all given through subcutaneous injections.

Adalimumab

Adalimumab (Humira®, Abbott, Chicago, IL, USA) is a fully humanized monoclonal antibody that inhibits TNF-α. It is administered in subcutaneous injections 40 mg every 2 weeks. When uveitis relapses still occur despite this dose, adalimumab may be administered weekly until achieving control of inflammation [38]. Several reports have showed the efficacy of adalimumab in treating a variety of uveitis conditions, including JIA-associated uveitis, sarcoidosis, Behçet’s and ankylosing spondilitis-associated uveitis [39-42]. Recently, Diaz-Llopis et al. conducted a prospective study of 131 patients with refractory uveitis treated with adalimumab [43]. This study showed statistically significant results regarding adalimumab efficacy in reducing anterior and vitreous inflammation, macular edema, immunosuppression and steroid loads, as well as improving visual acuity. Since adalimumab is a fully humanized antibody, it may offer superior side effect profile. Its most frequent side effect is the development of a self-limited cutaneous reaction at the injection site. Theoretically it has a lower risk of developing allergic reactions and anti-drug antibodies when comparing to infliximab. However, its effect is not as fast as infliximab, probably because of the subcutaneous route of administration. For this reason, we prefer using infliximab to induce rapid remission in the most sight-threatening and recalcitrant cases such as active Behçet’s uveitis. Once inflammation is controlled, then you can maintain remission with either infliximab or switching to another TNF antagonist with a subcutaneous administration, more comfortable both for the patient and for the physician (totally ambulatory, avoiding hospitalization).

Pediatric uveitis differs from uveitis seen in adulthood not only because of the uveitis presentation and severity of disease but also by a worse prognosis and age-specific problems that may occur under therapy. Adalimumab has advantages over infliximab in pediatric uveitis due to less infusion reactions and intolerance and better treatment compliance (Figure 2).

There are currently many clinical trials studying the efficacy and safety of adalimumab in non-infectious uveitis such as the ADUR trial (NCT00348153), VISUAL I, II and III (NCT01148225), and ADJUVITE (NCT01385826).

Golimumab

Golimumab (Simponi®, Abbott, Chicago, IL, USA) is a fully human monoclonal antibody that inhibits both free and transmembrane TNF-α. It is injected subcutaneously, 50mg every four weeks. Golimumab is a recent development in TNF antagonism and has been recently approved for the treatment of various rheumatic conditions [44]. Due to its molecular structure -a fully human monoclonal antibody- has a lower probability of developing neutralizing antibodies compared to other anti-TNF, thus decreasing the risk of an allergic infusion reaction and any loss of efficacy. Although fully human, resistance to golimumab may potentially develop as well [44]. Other advantages of golimumab over other TNF antagonists include the reduced dosing schedule, being a monthly subcutaneous self-administration. Recently, three papers have been published regarding golimumab use in uveitis [45-47] showing its efficacy in retinal vasculitis, JIA-associated uveitis, and Behçet’s disease. Further studies with longer follow-up to evaluate the long-term efficacy and safety of golimumab in a larger number of uveitis patients are warranted.

Certolizumab

Certolizumab (Cimzia®) consists only in the pegylated humanized Fab portion of a monoclonal antibody directed against TNF-α. Because its antibody structure lacks a constant region or Fc portion, there are limitations in certolizumab’s ability to fix complement or recruit antibody-dependent cell-mediated cytotoxicity [48]. Certolizumab has been approved for Crohn’s disease and rheumatoid arthritis in people who did not respond to standard therapy [49]. Certolizumab is dosed 400 mg subcutaneously 4 weeks after 3 dose-loading spaced every 2 weeks. Currently there are no studies demonstrating the efficacy of this drug in non-infectious uveitis.

Switching TNF Inhibitors

Acquired resistance to TNF antagonists may occur in the long term. In cases of refractory uveitis with loss of initial clinical response to one biological agent (secondary failure), switching to another agent can restore control of intraocular inflammation. In addition, switching helps controlling systemic symptoms and allows ease of administration. Why patients should respond to one biologic agent and not another, despite similar mechanisms of action, remains unexplained. Various possible hypotheses include differential bioavailability of these drugs and the development of anti-drug antibodies [50-52].

We consider infliximab and adalimumab as similar treatment options. They share a similar action profile but different routes of administration, immunogenic potential and therefore reason for using one or another should be related to nonclinical issues associated with the patient. Adalimumab appears to be effective and safe for treatment of refractory JIA-related uveitis, with a better performance in the medium-term period and it is more efficacious than infliximab in maintaining remission of chronic childhood uveitis.
<table>
<thead>
<tr>
<th>Generic name (trade name; sponsoring companies)</th>
<th>Format</th>
<th>Targets</th>
<th>Approved indications</th>
<th>Status in ophthalmology</th>
<th>Proposed mechanisms of action</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong> (Remicade; Janssen/ Biotech)</td>
<td>Chimeric IgG1</td>
<td>TNF-α</td>
<td>CD, UC, RA, PsA, AS and PPs</td>
<td>Approved for refractory Behçet’s uveitis in Japan since 2007</td>
<td>Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; induction of activated T cell and macrophage apoptosis</td>
<td>3-5 mg/kg iv infusion at 0, 2, and 6 weeks, followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg</td>
</tr>
<tr>
<td><strong>Adalimumab</strong> (Humira; Trudexa/ Abbott)</td>
<td>Human (phage-produced) IgG1</td>
<td>TNF-α</td>
<td>RA, JIA, PsA, CD, AS and PPs</td>
<td>Off-label. Phase III clinical trials ongoing for noninfectious uveitis</td>
<td>Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; lyses TNF-expressing cells by CDC; induction of activated T cell and macrophage apoptosis</td>
<td>40 mg every other week as sc injection; may increase to 40 mg weekly if no good control of ocular inflammation</td>
</tr>
<tr>
<td><strong>Certolizumab pegol</strong> (Cimzia; UCB)</td>
<td>Humanized Fab, PEG conjugate</td>
<td>TNF-α</td>
<td>CD, RA</td>
<td>Off-label</td>
<td>Neutralizes TNF activity by binding soluble and transmembrane and inhibiting binding to TNFRs</td>
<td>400 mg sc injection initially and at weeks 2 and 4, and then every 4 weeks</td>
</tr>
<tr>
<td><strong>Golimumab</strong> (Simponi; Janssen/ Biotech)</td>
<td>Human (mouse-produced) IgG1</td>
<td>TNF-α</td>
<td>RA, PsA and AS</td>
<td>Off-label</td>
<td>Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs</td>
<td>50 mg sc injection once a month</td>
</tr>
<tr>
<td><strong>Etanercept</strong> (Enbrel; Amgen/Pfizer)</td>
<td>TNFR2 ECD–Fc (IgG1) fusion protein</td>
<td>TNF-α and TNF-β</td>
<td>RA, JIA, PsA, AS and PPs</td>
<td>Off-label</td>
<td>Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs</td>
<td>50 mg once weekly as sc injection</td>
</tr>
</tbody>
</table>

**Abbreviations:** CD: Crohn’s Disease; UC: Ulcerative Cholitis; RA: Rheumatoid Arthritis; JIA: Juvenile Idiopathic Arthritis; PsA: Psoriatic Arthritis; PPs: Plaque Psoriasis; AS: Ankylosing Spondilitis; CCL: Chronic Lymphatic Leukemia; SC: Subcutaneous

**Table 1:** TNF antagonists.

**Figure 1:** Figure 1A shows a fundus photograph of case of Behçet’s disease with active posterior uveitis. There is vitreous haze and two retinal infiltrates in the posterior pole. Figure 1C shows an Optical Coherence Tomography demonstrating macular edema and abundant vitreous cells. These inflammatory signs rapidly resolved after initiating infliximab infusions (Figure 1B, D).
Figure 2: A case of Juvenile Idiopathic Arthritis-associated uveitis with band keratopathy, aphakia and 1+ cells in anterior chamber (A) and cystoid macular edema as shown in the Optical Coherence Tomography (B). After 2 months of adalimumab therapy macular edema has completely resolved (C).

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