Anti-Tumor Necrosis Factor-α Agents in Noninfectious Uveitis

Julie Gueudry\textsuperscript{a} · Phuc LeHoang\textsuperscript{b} · Bahram Bodaghi\textsuperscript{b}

\textsuperscript{a}Department of Ophthalmology, Charles Nicolle University Hospital, Rouen, and
\textsuperscript{b}Department of Ophthalmology, University of Paris VI, Pitié-Salpêtrière Hospital, Paris, France

Abstract

Anti-tumor necrosis factor-α (anti-TNF-α) agents represent a major breakthrough for the therapeutic management of different autoimmune conditions. Noninfectious uveitis may lead to various sight-threatening complications. Hence, from extrapolation of the benefit observed in autoimmune systemic diseases, anti-TNF-α agents are widely used in the treatment of noninfectious uveitis. However, their use remains mostly ‘off-label’in this indication, and the lack of evidence from randomized controlled studies limits a rationale choice. This review gives an update on the management of uveitis with TNF-α inhibitors, highlighting important issues, including initiation time, type of molecule, duration of therapy but also major adverse events.

Over the past 2 decades, therapy for a number of inflammatory diseases has developed into a highly differentiated approach with an increasing number of drug options. The introduction of anti-tumor necrosis factor-α (TNF-α) agents has revolutionized the treatment of rheumatic diseases such as rheumatoid arthritis, spondyloarthropathies and idiopathic juvenile arthritis as well as inflammatory bowel disease. Hence, anti-TNF-α agents have become a valuable addition to the therapeutic armamentarium for patients with refractory uveitis or intolerant to conventional treatment. However, due to the lack of evidence from randomized controlled trials, their use in uveitis remains ‘off-label’ in most countries. The purpose of this review is to stress current evidence on the use of these drugs, highlighting various possible choices of molecules and treatment strategies in intraocular inflammatory diseases.

Tumor Necrosis Factor-α

TNF-α is a highly potent proinflammatory cytokine with a wide range of activities in both inflammatory and immune responses. First characterized in 1985 \cite{1}, TNF-α
is synthesized by T helper cells and by activated macrophages, monocytes, neutrophils, and endothelial cells. It is primarily produced as a membrane-bound surface molecule, and a soluble form is created by proteolytic cleavage from the cell surface. It activates other cytokines, upregulates endothelial adhesion molecules, increases cell-mediated immunity and enhances granuloma formation and maintenance [2]. Therefore, TNF-α plays an important role in host defense against infectious agents. Particularly, data have suggested that TNF-mediated formation and maintenance of granuloma is fundamental for controlling *Mycobacterium tuberculosis* infection [3]. TNF-α achieves all its different cellular and pathological effects by its binding to either the TNFR1 (or p55) or TNFR2 (or p75) receptor subtype. TNF-α receptors on cells are stimulated by both soluble and transmembrane forms of TNF-α. However, soluble TNF-α mainly stimulates TNFR1 and membrane TNF-α mainly stimulates TNFR2 [2].

TNF-α is involved in the pathogenesis of many inflammatory disorders including noninfectious uveitis. Evidence for its pivotal role comes from experimental studies. A high TNF-α level was identified in the uvea and retina [4], in the aqueous humor and serum [5] of rats with endotoxin-induced uveitis. An intraocular high TNF-α level was identified in rats with experimental autoimmune uveitis [6, 7]. Moreover, intravitreal TNF-α injection in rabbits [8] and rats [9] was able to induce acute uveitis. There is evidence of raised TNF-α levels in ocular fluids of patients with uveitis [10, 11]. Interestingly, in endotoxin-induced uveitis, paradoxical effects of TNF blockage were also reported [12, 13].

**Anti-TNF-α Agents**

There are currently five anti-TNF-α agents available (table 1).

**Etanercept**

Etanercept is a fusion protein combining two human p75 TNF-α receptors. While both infliximab and adalimumab bind effectively to the soluble and transmembrane forms of TNF-α, etanercept forms less stable bonds with TNF-α, particularly the transmembrane form [14]. Etanercept does not appear to be an effective treatment for uveitis. Randomized controlled trials comparing etanercept with placebo in the treatment of chronic noninfectious uveitis [15], uveitis associated with juvenile idiopathic arthritis [16], and uveitis associated with sarcoidosis [17] found no benefit over placebo. Finally, retrospective studies showed that etanercept seems to be less efficacious than infliximab [18–20], as in a recent meta-analysis [21] of data from 4 placebo-controlled studies with anti-TNF agents in ankylosing spondylitis.
Infliximab

Infliximab is a murine-human chimeric antibody against TNF-α. It binds soluble and transmembrane forms of TNF-α with high affinity. The usual loading dose is 3–5 mg/kg body weight, intravenously, which can be increased to 10 mg/kg. Infusions are repeated after 2 and 6 weeks and, depending on clinical scores, every 4–8 weeks. Several studies reviewed infliximab efficacy in preventing uveitis relapses, in maintaining visual acuity and in the ability to taper corticosteroids and immunosuppressive agents [22, 23].

Adalimumab

Adalimumab is a fully humanized monoclonal antibody against TNF-α. It also binds to the soluble and transmembrane forms of TNF-α. Adalimumab has the technical
Advantage of a subcutaneous administration and is injected at a dosage of 40 mg every 2 weeks in adults. Since 2006, adalimumab has been used with positive results in refractory uveitis, and many types of uveitis seem to respond to adalimumab [24]. Moreover, the first prospective comparative study, however without randomization, between infliximab and adalimumab in childhood chronic uveitis suggests the potential superiority of adalimumab [25].

**New TNF-α Blockers**

Golimumab is a fully humanized anti-TNF-α monoclonal antibody, which is delivered monthly by the subcutaneous route. It binds to both soluble and transmembrane forms of human TNF-α. The constant regions of the heavy and light chains of golimumab are identical to those of infliximab in terms of the amino acid sequence. The variable region is specific for human TNF-α. It was approved in the United States in 2009 for use with methotrexate in adults with moderate to severe active rheumatoid arthritis and with or without methotrexate in adults with active psoriatic arthritis or active ankylosing spondylitis. In 2011, the two first cases of uveitis treated with golimumab were reported with encouraging results [26]. Certolizumab-pegol is a humanized PEGylated anti-TNF-α antibody. The pegylation of the antibody delays the elimination and thus provides a longer half-life. Certolizumab is the only TNF-α inhibitor that uses PEGylated technology. At the time of writing this chapter (December 2011), there is no scientific report on the use of certolizumab pegol in uveitis.

**Anti-TNF-α Agents: Treatment Indications for Use**

**Behçet’s Disease-Associated Uveitis**

Behçet’s disease (BD) is a chronic, relapsing, inflammatory disorder. Uveitis is one of the most severe complications of the disease. Visual prognosis has improved in recent years with the increasing use of immunosuppressive agents. Nevertheless, in a few cases, uveitis remains refractory to conventional therapy; and despite these aggressive strategies, blindness may occur. Recent results based on the use of anti-TNF agents highlight their significant efficacy [27]. Concerning the use of anti-TNF-α agents in BD, there is only one randomized, double-blind, placebo-control trial that evaluated the effect of etanercept on mucocutaneous manifestations and arthritis. Etanercept was beneficial for most of these manifestations, but no data about ocular involvement were available in that study [28]. Administration of infliximab for ocular inflammation in BD was first reported in 2001 [29]. The published evidence consists mainly of reports of the open use of infliximab, recently reviewed. Among these 158 reported patients, a rapid and dramatic improvement of visual acuity and decrease in ocular inflammation starting
24 h after infliximab was almost always reported [30]. A significant reduction in subsequent attacks of uveitis was achieved in 89% of these patients (65% was reported as complete). As BD is one of the most serious and sight-threatening clinical uveitis entities, infliximab was approved in Japan for the treatment of ‘Behcet’s disease complicated with refractory uveoretinitis, which does not respond to conventional therapies’ (Osaka, Japan, January 26, 2007, JCN Newswire) despite the lack of randomized controlled trials available. Moreover, the EULAR recommendations [31] on the treatment of BD were published including anti-TNF-α use. Infliximab dose of 10 mg/kg might not be superior to 5 mg/kg in efficacy and repeated infusions are needed [32]. The recommendations on the use of anti-TNF-α agents in BD by an expert panel explained that in acute, unilateral, posterior uveitis with significant reduction in visual acuity (<20/100), as well as in cases with inflammation at the level of the macular area and those with bilateral involvement, infliximab could be used as a first-line agent to achieve a fast-onset response. In patients with two or more relapses/year despite, or intolerant to, adequate doses of azathioprine and/or cyclosporin A, or, interferon (IFN)-α2a, combined with prednisolone (<7.5 mg/day), infliximab can be used as a maintenance regimen [27]. However, it is important to note that there are no data supporting continuous use of infliximab as a monotherapy [27]. Even though IFN-α2a seems to be an alternative to anti-TNF-α drugs [33], anti-TNF-α seems to be appropriate, particularly in case of IFN-α2a failure [27, 29, 34, 35]. Use of anti-TNF-α agents in BD was principally evaluated as an add-on therapy. Actually, at initiation of treatment with infliximab, concomitant administration of immunosuppressive agents was discontinued in some studies, whereas corticosteroid therapy was not [30]. Nonetheless, a prospective comparative study comparing different treatment approaches for acute panuveitis attacks in BD have been recently reported [36]. It shows that infliximab (5 mg/kg), when given at the onset of an acute panuveitis attack, exerts a significantly faster and more effective effect in suppressing ocular inflammation than intravitreal triamcinolone (4 mg) or high-dose methylprednisolone (3-day course, 1 g/day). Given that control of acute ocular inflammation in BD is mandatory to avoid permanent visual loss, an intravenous infliximab infusion should be always considered for panuveitis attacks in BD. Few reports on adalimumab in BD-associated uveitis, have been published. However, it was used with success in case series [37–39] and in a recent retrospective study. In this study, 10 out of 11 patients showed complete resolution of inflammation by 4 weeks [40]. Although more complete evidence is needed, particularly in the long-term efficacy and its use as a first-line therapy [41, 42], numerous publications suggest that infliximab represents an important therapeutic advancement in BD-associated uveitis. A therapeutic algorithm is proposed in figure 1.

**Spondyloarthropathies and B27-Associated Uveitis**

Uveitis is a well-known extra-rheumatologic manifestation of spondylarthropathies (including ankylosing spondylitis, AS, and psoriatic arthritis). A single
Infusion of infliximab may be effective in treating an acute uveitis attack, but does not seem to affect disease recurrence [43]. In this indication, anti-TNF-α usefulness seems to be limited given that acute anterior uveitis generally responds to intensive corticosteroid therapy. A minority of cases could be managed with anti-TNF-α agents for chronic ocular complications which include posterior segment involvement or chronic disease refractory to conventional therapy [44]. The main interest of anti-TNF-α agents in this indication lies in preventing uveitis relapses. The effect of anti-TNF-α agents on anterior uveitis relapses in AS was analyzed in one large retrospective study [45] and in one meta-analysis of four clinical trials, three of which were placebo-controlled, randomized trials [21]. The retrospective study suggested that infliximab and adalimumab reduced the rate of uveitis, while the frequency of uveitis in patients with AS treated with etanercept remained unchanged [45]. In the meta-analysis, infliximab and etanercept therapies seem to reduce the incidence of uveitis even though infliximab appeared to be more effective than etanercept. However, the differences between infliximab and etanercept did not reach statistical significance (p = 0.08). Adalimumab was evaluated in a prospective open-label study showing its efficacy to prevent uveitis relapses in AS [46]. Hence, the use of an anti-TNF-α antibody should be considered first rather than using a soluble TNF receptor, in spondyloarthritis patients with a history of uveitis.

**Fig. 1.** Proposed algorithm for the treatment of BD-associated uveitis with posterior segment involvement. Ct = Corticosteroids; IS = immunosuppressive agents; Aza = azathioprine; CycA = cyclosporin A.
Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a disease of unknown etiology that begins before the age of 16 years and persists for at least 6 weeks. JIA is a clinically heterogeneous group of diseases. The classification scheme developed by the International League of Associations of Rheumatologists in 2001 differentiates seven subtypes of JIA [47]. The risk of uveitis is highest in oligoarticular onset and extended oligoarticular forms [48]. The medical treatment of uveitis is challenging. Systemic corticosteroid therapy is often required, and immunomodulatory therapy is often needed in order to preserve visual acuity and to prevent significant morbidity of chronic steroid administration. Anti-TNF-α agents have been used with positive results. Although one previous study reported that etanercept had some efficacy in the treatment of chronic uveitis in children, subsequent studies failed to demonstrate a benefit [49]. A randomized placebo-controlled study of etanercept in patients with uveitis found no evidence of efficacy [16]. Furthermore, data from the German etanercept registry [50] showed insufficient control of uveitis by etanercept, whereas arthritis was well controlled. Multiple studies describe the efficacy of infliximab and adalimumab in JIA-associated uveitis [19, 51–54]. Recently, a prospective comparative study between infliximab and adalimumab in 33 children with refractory chronic uveitis (22 children with JIA) has been published. This study, without randomization, suggests that adalimumab is as efficacious as infliximab in a short-term period (31 of 33 children achieved complete remission), but maintains in remission for a longer period and with a higher rate. At 40 months, 9 (60%) of 15 children receiving adalimumab compared to 3 (18.8%) of 16 children receiving infliximab were still on remission (p < 0.02) [25]. This suggests the potential superiority of adalimumab in JIA-associated uveitis as previously hypothesized [55]. As in HLA-B27-associated uveitis, the use of infliximab and adalimumab should be considered first rather than using etanercept, in JIA patients with a history of uveitis.

Sarcoidosis

The first study mentioning successful anti-TNF-α use in steroid-resistant sarcoidosis was published in 2001 [56]. However, a placebo-controlled randomized study conducted to evaluate the safety and effectiveness of infliximab in subjects with chronic pulmonary sarcoidosis has not produced the expected results [57, 58]. Another randomized placebo-controlled study suggests that infliximab may be beneficial in the treatment of extrapulmonary sarcoidosis in patients already receiving corticosteroids, but authors found no improvement in patients with ocular disease who received infliximab [59]. Nevertheless, infliximab appears to be effective in ocular sarcoidosis, although data are limited to a case series [59] and to cases reports [25, 60, 61]. However, it is quite necessary to take into account the fact that sarcoidosis is underdiagnosed and a number of presumed, probable or possible sarcoid uveitis are labeled ‘idiopathic’ and may respond
to anti-TNF-α [23]. Etanercept did not appear effective [17]. Adalimumab was successfully used recently in patients with uveitis and papillitis [62].

**Uveitis Associated with Other Conditions**

Few isolated cases of refractory Vogt-Koyanagi-Harada disease treated with infliximab were published with encouraging results [63–65]. Furthermore, infliximab was also used in pediatric forms [66] and adalimumab was used in a refractory case [67]. Successful use of infliximab in sympathetic ophthalmia has been reported in a few case reports [68–70]. Variable results induced by infliximab have been observed in birdshot chorioretinopathy [60, 61, 65, 71], in multifocal choroiditis [60, 72], and in idiopathic retinal vasculitis, aneurysm, and neuroretinitis syndrome [73]. Infliximab was used in a patient with refractory serpiginous choroiditis with a good clinical outcome. However, this patient died of disseminated tuberculosis (TB) after treatment [74]. Infliximab was also beneficial in patients with idiopathic refractory uveitis [51, 60, 75, 76] and diffuse subretinal fibrosis syndrome [77]. Etanercept has no significant efficacy over placebo in preventing relapses of idiopathic uveitis [15]. Adalimumab was able to control ocular inflammation in idiopathic refractory uveitis [25, 37].

**Adverse Events**

Anti-TNF-α agents in patients with uveitis seem well tolerated except for one study [60], but long-term studies on safety in uveitis are still missing. Safety profile of anti-TNF-α agents in rheumatoid arthritis is well known, and data could be extrapolated by taking into account the fact that differences between safety profiles according to different diseases were noted.

**Infections**

Anti-TNF-α agents carry a specifically increased risk of TB, usually reactivations of latent disease [78] but also primary infection. Important differences in the risk of latent TB reactivation exist, with the risk being higher with infliximab and adalimumab than with etanercept [79, 80]. Screening for latent TB and prophylactic anti-TB for all those found positive is recommended for all patients planning to initiate therapy with anti-TNF-α agents. The role of new screening tests for TB (Quantiferon and T-spot) has not been fully validated in this indication even though they can improve sensitivity in the immunosuppressed host and specificity in patients who have received Bacille Calmette-Guérin immunization. Finally, clinical similarities between ocular TB and other uveitis entities, such as choroidal TB and serpiginous choroidopathy [74],
highlight the importance of ruling out TB in all refractory uveitis before initiating an anti-TNF-α therapy. Various and severe non-TB opportunistic infections, especially those with intracellular micro-organisms, may develop in patients receiving anti-TNF-α treatment. Furthermore, infliximab and adalimumab rather than soluble TNF receptor therapy and steroid use >10 mg/day were reported to be independently associated with opportunistic infections [81]. The safety profile of anti-TNF-α agents in the setting of hepatitis C infection seems to be acceptable, even though close monitoring of serum amino-transaminases should be performed during treatment. However, for patients with hepatitis B, concomitant anti-viral treatment would be recommended [82].

**Demyelination**

Several demyelinating and neurologic events, including exacerbations of pre-existing multiple sclerosis and optic neuritis, were reported implicating infliximab, adalimumab and etanercept [83–87]. Hence, anti-TNF-α therapy should not be given when there is a clear history of multiple sclerosis; it should be used with caution for other demyelinating diseases, and withdrawn if demyelination occurs [82]. Furthermore, it seems appropriate to recommend brain MR imaging to exclude multiple sclerosis in patients with intermediate uveitis and retinal vasculitis before receiving anti-TNF-α therapy.

**Others**

There is no conclusive evidence for an increase in risk of solid tumors or lymphoproliferative diseases with anti-TNF-α agents, although vigilance is required [82]. Development of antinuclear antibodies and autoantibodies against double-stranded DNA has previously been reported in response to etanercept, infliximab and adalimumab, but may be more common with infliximab. However, ‘full-blown’ anti-TNF-induced lupus or vasculitis is rare [88]. Injection site reactions occur with the use of etanercept, adalimumab, certolizumab pegol and golimumab. Infliximab can induce the formation of neutralizing antibodies, resulting in loss of efficacy and the appearance of infusion reactions [89]. Furthermore, antibodies have been also reported, to a lesser extent, against adalimumab, certolizumab pegol and golimumab. In most of cases, a conventional immunosuppressive agent such as methotrexate is associated with the treatment in order to prevent this complication. New onset and worsening of congestive heart failure have been reported, hence anti-TNF-α agents should not be initiated in patients with moderate and severe cardiac failure and should be used with caution in patients with mild cardiac failure [82]. Hematological complications associated with anti-TNF-α therapy are rare.
Paradoxical Adverse Events

A rare and paradoxical adverse event is the development of sarcoidosis during treatment with infliximab, adalimumab and etanercept [90–93]. Paradoxical occurrence of psoriasis has also been reported [94]. The issue of whether anti-TNF agents cause ocular inflammation remains a matter of debate [95]. There are several case reports of uveitis developing in patients treated with anti-TNF-α therapy. Most cases have been reported with etanercept [96–102]. However, as etanercept was shown to be less effective than anti-TNF-α antibodies to prevent and to control uveitis, does it induce uveitis or does it only fail to prevent their occurrence? Nonetheless, Lim et al. [95] reported 26 cases of uveitis presumably associated with anti-TNF-α in which no known condition predisposing to uveitis was identified. However, authors conceded that there was limited information available on the clinical diagnosis. Especially in the case of granulomatous uveitis, occurrence might be due to a potential sarcoidosis associated with anti-TNF-α [90]. Therefore, even though more data are required, switch for infliximab and adalimumab may be warranted when a patient develops uveitis during etanercept therapy.

Ocular Surgery

The French Rheumatology Society recommends interrupting TNF-α therapy for two half-lives before surgery in a sterile setting such as cataract surgery. However, very few data concerning cataract surgery in uveitis patients under anti-TNF-α are available, and the potential benefit of preventing postoperative infections by stopping treatment should be balanced against the risk of a perioperative intraocular inflammation recurrence. Up to now, few patients receiving infliximab for BD-associated uveitis were reported. Cataract surgery was performed without any complications 1 and 4 weeks after anti-TNF-α agents [103–105].

‘Switching’ Anti-TNF-α Agents

Switching between anti-TNF-α agents may be necessary. Efficacy and safety of switching between anti-TNF-α therapies have been well studied in other diseases. There is little evidence that ‘switching’ helps to gain or maintain uveitis remission. Nonetheless, case reports and a case series concerning BD and JIA-associated uveitis suggest that switching infliximab to adalimumab was successful to control uveitis in case of inefficacy [52, 106, 107], in case of intolerance or to avoid repeated injections [34, 108].
**Future Directions**

A topically applied TNF-α inhibitor single-chain antibody named ESBA105 is under development for patients suffering from acute anterior uveitis. In a prospective series of 5 patients with refractory uveitic macular edema, intravitreal adalimumab was not successful in reducing central retinal thickness and improving visual acuity [109]. In this study, no ocular or systemic adverse events were observed. Nevertheless, contradictory results about safety of intravitreal adalimumab injections have been published [109–112]. Intravitreal infliximab injections were not tested up to now in uveitis treatment. However, contradictory results concerning its safety have been published [113–115]. Further studies focusing on the concentration and toxic effects of intravitreal injections of anti-TNF-α agents are necessary, although their efficacy remains uncertain.

**Conclusions**

Anti-TNF-α agents are widely used for the treatment of noninfectious uveitis even though it remains mostly an off-label use. The lack of evidence from randomized controlled studies in the uveitis area limits a rationale choice and initiation time of anti-TNF-α therapy, the molecule type and duration of treatment. Furthermore, this is a rapidly changing field with new data emerging regularly. Nevertheless, to the best of our knowledge, a few issues may be addressed.

**Which one?** There are no head-to-head randomized comparative studies comparing efficacy of anti-TNF-α agents in uveitis area. Nevertheless, etanercept should not be used in case of uveitis. Adalimumab might appear as the most favorable anti-TNF-α agents because of its facility of administration, its low rate of neutralizing antibodies induction and its possible superior efficacy to maintain in remission chronic refractory uveitis in children. One limitation with adalimumab may be its lower efficacy on different rheumatic conditions, compared with infliximab. As golimumab requires less frequent injections, it might have potential application in uveitis area if its efficacy and its side effect profile do not differ from the first-generation agents.

**When?** After ruling out ocular TB and latent TB, anti-TNF-α agents could be used as a third-line treatment in chronic refractory uveitis as maintenance therapy. However, in rescue therapy, infliximab infusion may be considered particularly in BD-associated uveitis, and anti-TNF-α maintenance therapy might be considered earlier to avoid drug-induced side effects particularly in children.

**How Long?** Currently, no response is available. However, anti-TNF-α therapy seems to be well tolerated with a relatively few side effects. Given collective clinical experience in uveitis and other conditions, switching between anti-TNF-α therapies appears to be efficacious and safe in cases of primary or secondary failure permitting to prolong their use. Compared with other biologic agents such as IFN-α, treatment with anti-TNF-α induces remission, but relapses occur very frequently after discontinuation.
**References**


