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Chapter

Tumor Necrosis Factor-Alpha Inhibitory Therapy for Non-Infectious Autoimmune Uveitis

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Abstract

Biologic agents represent a mainstay in the treatment of refractory non-infectious, immune-mediated uveitis. Tumor necrosis factor (TNF)-α inhibitors have demonstrated efficacy in inducing and sustaining disease remission in numerous systemic inflammatory disorders and their associated uveitic entities. In particular, studies have shown that infliximab and adalimumab can induce steroid-free disease remission in patients with Behçet's disease and juvenile arthritis as treatments that are superior to conventional disease-modifying immunosuppressive agents. Patients receiving anti-TNF-α therapy may experience adverse events and should be closely monitored for the development of opportunistic infections, reactivation of tuberculosis and hepatitis, demyelinating disease and neuropathies, as well as malignancies.

Keywords: TNF-alpha inhibitors, uveitis, ocular inflammation, etanercept, infliximab, adalimumab, golimumab, certolizumab

1. Introduction and overview

- *Mechanism of action*: TNF-α inhibitors suppress the robust systemic and ocular inflammatory response triggered by tumor necrosis factor.

- *Formulations & application to uveitis*: the currently available agents include etanercept, a TNF receptor fusion protein that binds TNF-α and TNF-β, as well as monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab that bind and neutralize soluble and transmembrane TNF. TNF-α inhibitors have been used efficaciously in uveitis associated with systemic disease, most notably Behçet's disease and juvenile idiopathic arthritis, as well as idiopathic intermediate, posterior and panuveitis.

- *Adverse effects*: important side effects of TNF-α inhibitors include malignancy (lymphomas, skin cancer), infections (reactivation of latent tuberculosis and hepatitis, fungal and various opportunistic infections), demyelinating disease, congestive heart failure, induction of auto-antibodies, and injection site reactions.

- *Monitoring clinical response and serum anti-drug antibodies*: a major concern in patients who demonstrate suboptimal response or fail anti-TNF-α therapy is the development of drug antibodies, which may warrant switching agents to either another TNF antagonist, or alternative immunosuppression.

2. Mechanism of action

2.1 Physiology of TNF

Tumor necrosis factors are pro-inflammatory cytokines that play an integral role in innate and adaptive immunity. These factors exist in two forms as TNF-α and TNF-β (or lymphotoxin), and were named for *in vitro* observations of their induction of tumor cell lysis and necrosis [1]. Also referred to as sentinel cytokines or "the body's fire alarm," TNFs have since been discovered to initiate the host defense response to local injury and infections, notably those caused by mycobacterial, fungal, and other opportunistic pathogens. TNFs are also responsible for formation of lymphoid tissue, as well as activation and recruitment of leukocytes, including neutrophils and macrophages for granuloma formation [2]. The physiologic functions of TNF explain many of the adverse effects associated with TNF blockade, including cytopenias; increased risk for infection, particularly reactivation of hepatitis and tuberculosis; as well as higher incidence of certain malignancies, discussed in more detail later in this chapter. Regulation of TNF is intricate, and encompasses a variety

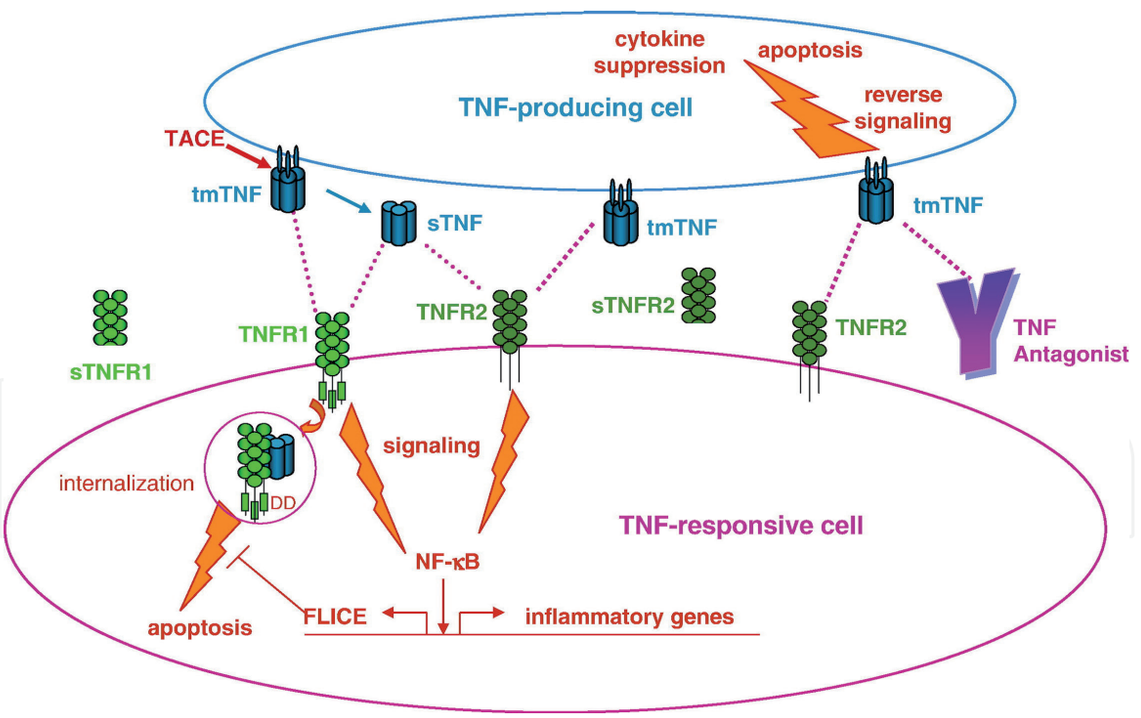


Figure 1.
TNF production, receptor interaction, and signaling (taken with permission from Tracey et al. [2]). Stimulation of a TNF-producing cell (top) results in cell surface expression of tmTNF trimers and enzymatic cleavage by TACE to release sTNF. Both tmTNF and sTNF can bind to cell surface TNFR1 or TNFR2 on a TNF-responsive cell (bottom), initiating signaling pathways that lead to apoptosis or NF-κB activation and inflammatory gene activation. The induction of apoptosis by sTNF via TNFR1 involves internalization of the ligand-receptor complex and association of death domains (DD) in the cytoplasmic tail of TNFR1 with adapter proteins and is normally blocked by FADD-like IL-1β–converting enzyme (FLICE). Reverse signaling can be initiated by TNFR2 or TNF antagonist binding to cell surface tmTNF, resulting in cytokine suppression or apoptosis. Soluble TNF receptors (sTNFR1 and sTNFR2) can be released from a TNF-responsive cell following enzymatic cleavage. TNF antagonists bind sTNF and tmTNF to neutralize their effects. TACE = tumor necrosis factor-alpha converting enzyme; NF-κβ = nuclear factor kappa β.

of stimuli, TNF-producing and responsive cells, and feedback loops. Numerous immune cells, including activated macrophages, T cells, mast cells, granulocytes, and natural killer cells, produce TNF in the form of transmembrane TNF (tmTNF) and soluble TNF (sTNF), which is cleaved from tmTNF (**Figure 1**). Initial production of these factors may be triggered by a wide array of stimuli, including microbial pathogens, tumor cells, immune complexes, other cytokines, complement factors, irradiation, ischemia or hypoxia, and trauma [2].

Ultimately, both tmTNF and sTNF act upon TNF-responsive cells to trigger an inflammatory response via membrane-bound TNF receptors 1 and 2 (TNFR1 and TNFR2). TNFR1, also known as p55, is constitutively expressed on nearly all cell types except erythrocytes. Depending on the metabolic state of the cell, binding of TNFR1 triggers one of two distinct signaling pathways: (1) activation of nuclear factor kappa-β, a family of transcription factors that controls many inflammatory genes, or (2) caspase-dependent apoptosis [2]. TNFR2, also known as p75, is preferentially expressed on endothelial and hematopoietic cells, and some tumor cells. The subsequent pathways at this time are not as well delineated as those for TNFR1, but ongoing studies suggest TNFR2 mediates the activity of regulatory and effector CD8+ T cells, as well as interleukin production by B cells [3, 4]. In the eye, pigment epithelial cells of the iris, the ciliary body, and retina locally express TNFR1 and TNFR2.

Positive and negative feedback loops initiated by TNF-induced factors regulate TNF production. Proteolytic cleavage of the extracellular domain of membrane-bound TNF receptors results in soluble TNF receptors, which bind and neutralize

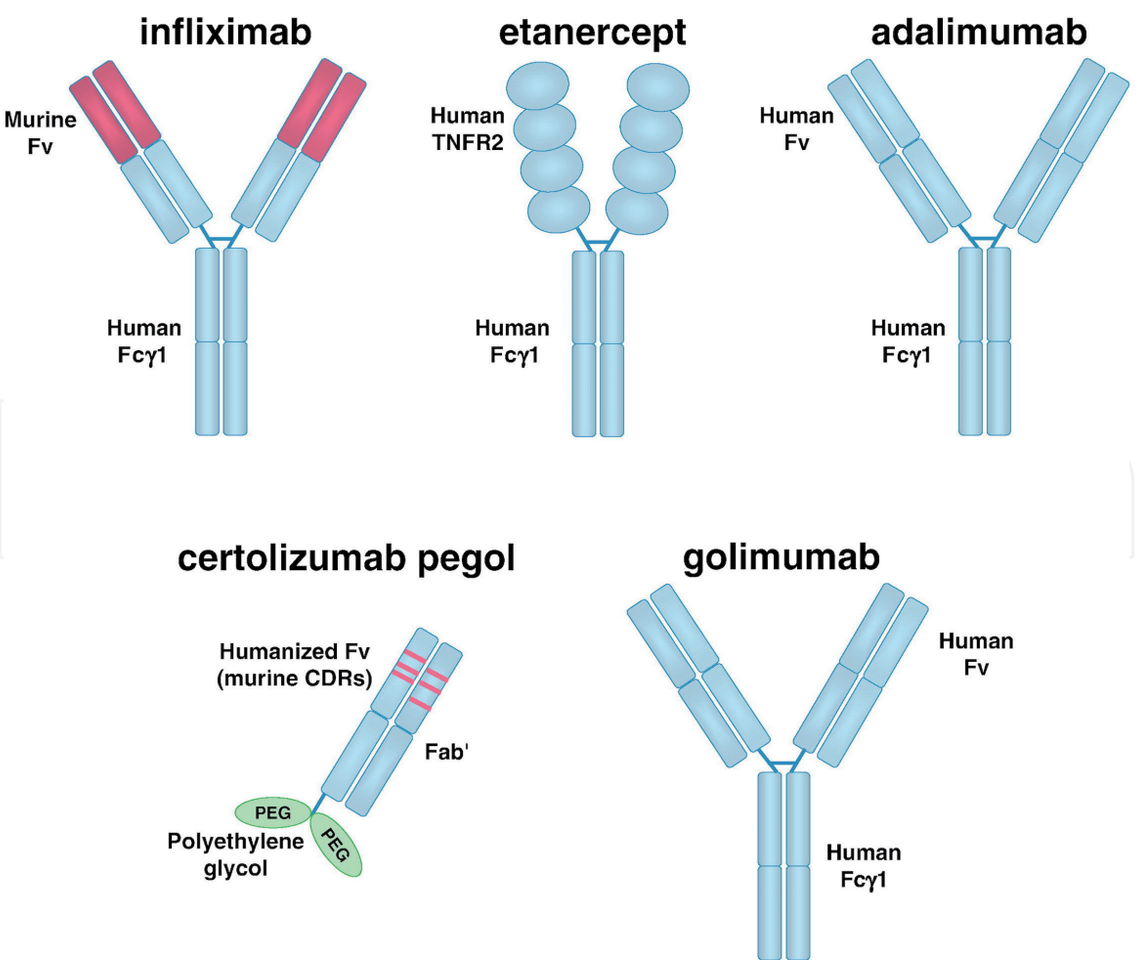


Figure 2.
Downstream effects of TNF depicting the common cascades leading to immune regulation, apoptosis, and inflammation (center), as well as biologic activities specific to the pathophysiology of Crohn's disease, rheumatoid arthritis, and psoriasis (taken with permission from Tracey et al. [2]).

TNF without inciting inflammation [5]. This maintains the amount of circulating TNF below pathologic limits, and thus healthy individuals do not typically express detectable serum levels of these factors.

2.2 TNF blockade

In immune-mediated disease, high concentrations of TNF induce excessive systemic inflammation and organ injury via direct pathogenic effects and production of other inflammatory mediators, apoptosis, and tissue destruction (**Figure 2**). TNF-α has been implicated in the pathogenesis of not only uveitis, but also commonly associated complications of ocular inflammation, including cystoid macular edema and choroidal neovascularization. Increased expression and production of TNF-α has been found to be crucial in the induction phase of experimental autoimmune uveitis, and inhibition of TNF-α in these experimental models of uveitis reduces the incidence and severity of intraocular inflammation [6].

Given the key role of TNF as a mediator of inflammation, its potential as a pharmaceutical target for blockade has been recognized, and several agents that antagonize TNF and TNF receptors have been created. Etanercept, the sole inhibitor in its class that is not a monoclonal antibody, is a soluble dimeric fusion protein

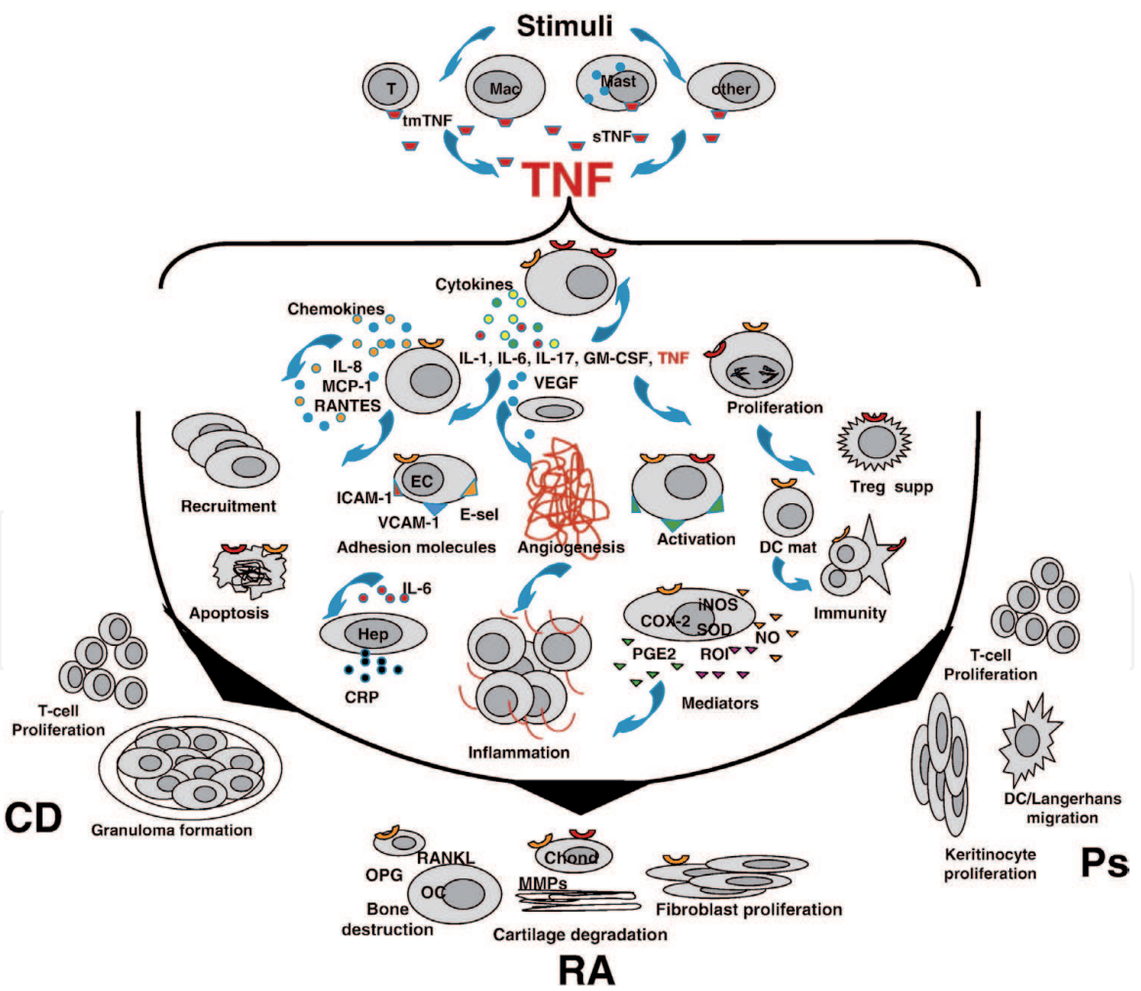


Figure 3.
Molecular structures of the available TNF inhibitors (taken with permission from Tracey et al. [2]). Infliximab is a mouse/human chimeric monoclonal anti-TNF antibody of IgG1 isotype. Adalimumab and golimumab are fully human IgG1 monoclonal anti-TNF antibodies. Etanercept is a fusion protein of TNFR2 (p75) and the Fc region of human IgG1. Certolizumab is a PEGylated Fab' fragment of a humanized IgG1 monoclonal anti-TNF antibody. Fv = variable fragment domain; Fcγ1 = crystallizable fragment domain of IgG1; CDR = complementarity determining region.

that carries two copies of the ligand-binding portion of the TNF receptor p75 linked to the crystallizable fragment (Fc) region of human immunoglobulin G (IgG). This forms unstable complexes with and transiently neutralizes both TNF-α and TNF-β, in contrast to the other agents that bind only TNF-α.

The remainder of this class comprises monoclonal antibodies that bind both sTNF and tmTNF, with certain structural variations between agents (**Figure 3**). Infliximab is a chimeric mouse-human monoclonal antibody, with murine fragment antigen-binding regions (Fab) that bind soluble and bound TNF-α to inactivate them. Adalimumab and golimumab, on the other hand, also bind soluble and transmembrane forms of TNF-α, but are fully human; the absence of non-human components renders them less immunogenic and, therefore, less subject to the formation of anti-drug antibodies as compared to infliximab. Similarly, certolizumab pegol is humanized, but is also distinct from the others in that this compound couples the Fab region to polyethylene glycol rather than the Fc region of human IgG. This reduces the antigenicity of this agent and increases the half-life of the drug [7]. The absence of the Fc portion of human IgG also precludes the typical antibody effector functions of complement activation, apoptosis induction, and neutrophil degranulation [2]. Further information regarding each of these agents is detailed in the section below.

3. Formulations and their application to uveitis

Currently, TNF inhibitors are approved by the United States Food and Drug Administration (FDA) for use in many immune-mediated conditions, including rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis and psoriatic arthritis. Only adalimumab has been approved currently by the FDA for non-infectious intermediate, posterior and panuveitis in adults and children older than 2 years of age. Though their use for uveitis is considered off-label, the remaining anti-TNF agents have been routinely used to control ocular inflammation associated with systemic disease. These medications have been found to be particularly effective in Behçet's disease and juvenile idiopathic arthritis, as well as intermediate, posterior, and panuveitis of idiopathic and other causes. In general, initial response to TNF-α inhibitors is more rapid than other immunomodulatory agents, which can take several weeks to months to become therapeutic. Recommendations regarding administration and dosing of these agents are not specific to the treatment of uveitis, but are derived from rheumatologic literature. **Table 1** summarizes the available TNF antagonists.

3.1 Etanercept

Etanercept (Enbrel®, Amgen Wyeth, Immunex Corporation, Thousand Oaks, CA, USA) was the first anti-TNF-α agent to be approved by the FDA in 1998 for use in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. The compound consists of a humanized, recombinant dimeric fusion of a human Fc molecule and two p75 TNF receptors. By binding circulating TNF-α and TNF-β, etanercept prevents binding of these factors to cell surface TNF receptors and the subsequent pro-inflammatory cascade. Of note, unlike other agents within its class, etanercept does not bind tmTNF, and thus does not induce lysis of TNF-producing cells.

3.1.1 Administration

Etanercept is administered as subcutaneous injections dosed 50 mg once weekly or 25 mg twice weekly. Higher doses may be used short term in some conditions.

	Etanercept (Enbrel)	Infliximab (Remicade)	Adalimumab (Humira)	Golimumab (Simponi, Simponi Aria)	Certolizumab (Cimzia)
Structure and mechanism of action	Dimeric fusion protein of TNF receptors that binds TNF-α and TNF-β	Chimeric mouse-human monoclonal antibody that binds TNF-α	Fully humanized monoclonal antibody that binds TNF-α	Fully humanized monoclonal antibody that binds TNF-α	PEGylated antigen-binding fragment that binds TNF-α
Route of administration and dosages	Subcutaneous injection (50 mg weekly or 25 mg twice weekly)	Intravenous infusion (loading: 3–5 mg/kg at 0, 2, and 6 weeks; maintenance: 3–10 mg/kg monthly every 4–8 weeks, up to 20 mg/kg monthly in children)	Subcutaneous injection (80 mg loading dose, followed by 40 mg every 1–2 weeks)	Subcutaneous injection (50 mg monthly) or intravenous infusion (loading: 2 mg/kg at weeks 0 and 4; maintenance: every 8 weeks)	Subcutaneous injection (loading: 400 mg at weeks 0, 2, and 4; maintenance: 400 mg injections monthly, or 200 mg injections every other week)
Approved indications	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis	Noninfectious intermediate, posterior and panuveitis; rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	Rheumatoid arthritis
Adverse events	Opportunistic and invasive fungal infections, reactivation of underlying hepatitis and tuberculosis infections, malignancies (lymphoma, skin cancers), demyelinating disease, congestive heart failure, induction of autoimmunity				

Table 1.
Summary of the available TNF inhibitors, their structures and mechanisms of action, routes and dosages of administration, and adverse effects.

3.1.2 Efficacy

Etanercept appears to be inferior to infliximab and adalimumab for the control of ocular inflammation and is generally considered inadequate for the treatment of uveitis [8]. It should be noted that the present data are mostly small series, and no large, prospective head-to-head studies exist comparing effectiveness or safety across the TNF-α antagonists. However, use of etanercept has consistently shown decreased initial response, greater corticosteroid burden, and higher rates of disease recurrence than have been reported with the use of infliximab for uveitis [9]. Furthermore, etanercept has been associated with the paradoxical development of *de novo* uveitis and induction of uveitis flares in patients with spondyloarthropathies, rheumatoid arthritis, juvenile idiopathic arthritis, and sarcoidosis [10]. The mechanism for this is unclear, but is thought to be related to pharmacokinetic

differences between etanercept and other TNF inhibitors, or differences in reverse signaling, such as cytokine modulation [2].

3.1.3 Safety

A recent prospective analysis of etanercept, infliximab, and adalimumab found that the rate of infection requiring hospitalization, intravenous antibiotics, or life-threatening complications or disability is lower with etanercept than with infliximab or adalimumab [11].

3.2 Infliximab

Infliximab (Remicade®, Janssen Biotech, Inc., Horsham, PA, USA) was the second anti-TNF-α agent to receive FDA approval in 1999 for treatment of rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. This drug is a chimeric mouse-human monoclonal antibody that binds and neutralizes both circulating and membrane-bound TNF-α.

3.2.1 Administration

Infliximab is only available as an intravenous infusion. Typical loading regimens involve initial doses of 3–5 mg/kg at 0, 2, and 6 weeks, though the loading dosages may vary based on disease etiology and severity. Once a steady state has been achieved following the loading period, patients undergo regular infusions approximately every 4–8 weeks. Maintenance doses may be safely increased to 5–10 mg/kg monthly, though in JIA, children may require higher doses (up to 20 mg/kg) to successfully quell disease [12].

3.2.2 Efficacy

Numerous studies have established the efficacy of infliximab in various etiologies of uveitis, with the most data supporting its use in Behçet's disease and juvenile idiopathic arthritis. Consistently, infliximab is associated with a decrease in the mean corticosteroid dose and immunosuppression load required for management of ocular inflammation. Patients with Behçet's disease-related uveitis and retinal vasculitis have been shown to achieve faster resolution of disease with infliximab than with local and systemic corticosteroid therapy, or other immunomodulatory agents [13, 14]. Markomichelakis et al. performed a prospective, observational study of patients with panuveitis secondary to Behçet's disease who received a single dose of infliximab infusion of 5 mg/kg, high-dose methylprednisolone 1 g/day for 3 days, or intravitreal triamcinolone; infliximab was found to be superior to other treatments in terms of decreasing ocular inflammation, and clearing retinal vasculitis, retinitis, and cystoid macular edema [13]. Many children with JIA and chronic refractory noninfectious uveitis also achieve improvement as well as quiescence of disease with the addition of infliximab to methotrexate [15]. A review of 16 children on concomitant infliximab (mean dose 8.2 mg/kg with a median interval of 5.6 weeks between infusions) and methotrexate therapy found that this regimen effectively controlled ocular inflammation over 1 year of follow-up, without recurrence of uveitis in 58% of patients [15]. Reports also suggest efficacy of infliximab in the treatment of uveitis related to many other conditions, including spondyloarthropathies, inflammatory bowel disease, psoriasis, Takayasu disease, pars planitis, multifocal choroiditis, birdshot chorioretinopathy, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and idiopathic uveitis. Infliximab use

has also shown benefit in recalcitrant uveitic cystoid macular edema and diffuse subretinal fibrosis [16, 17]. In a study of nine patients with uveitis-related cystoid macular edema refractory to conventional immunosuppressive therapy, Schaap-Fogler et al. reported that after transitioning to infliximab (dosage of 5 mg/kg at 0, 2, and 6 weeks, followed by administration every 6–8 weeks afterward) or adalimumab (dosage of 40 mg every 2 weeks), patients experienced improvement in central macular thickness and visual acuities comparable to those on conventional immunomodulatory therapy on follow-up at 3, 6, and 12 months [16].

In a small percentage of patients, the formation of human anti-chimeric antibodies, or HACA, may neutralize infliximab and limit its duration of effect. Other immunomodulatory agents may be administered concurrently with infliximab to reduce the rate of HACA formation. Further discussion regarding the development of HACA and approach to patients who have failed therapy is detailed in the section "Adverse effects."

3.2.3 Safety

Infliximab has been associated with significant adverse effects, including serious infections, congestive heart failure, pulmonary embolus, induction of autoantibodies, as well as development of a rare lupus-like syndrome [11, 18].

3.3 Adalimumab

Adalimumab (Humira®, AbbVie Inc., North Chicago, IL, USA) is a fully humanized monoclonal antibody against TNF-α. Since its approval by the FDA in 2002, it has been steadily gaining popularity for its efficacy and relative safety, and now serves as a preferred agent within its class. At this time, its approved indications include treatment of rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, and juvenile idiopathic arthritis. In 2016, it was approved by the FDA for treatment of non-infectious intermediate, posterior and panuveitis.

3.3.1 Administration

Adalimumab is delivered in the form of subcutaneous injections with a loading dose of 80 mg followed by 40 mg injections at weekly or biweekly intervals.

3.3.2 Efficacy

Numerous studies have shown adalimumab to be efficacious, particularly in uveitis associated with spondyloarthropathies, HLA-B27 positive status, and juvenile idiopathic arthritis. There also exists moderate-quality evidence for the efficacy of adalimumab in Behçet's disease-associated uveitis, pars planitis, and idiopathic posterior uveitis. A multinational randomized controlled trial evaluating adalimumab for the treatment of active noninfectious intermediate, posterior, or panuveitis despite prednisone therapy revealed significant improvement in anterior and posterior chamber inflammation as well as visual acuity [19]. Compared to placebo, adalimumab achieved early and sustained disease control after discontinuation of glucocorticoid treatment, with less chance of treatment failure and increased median time to treatment failure (24 weeks in adalimumab group versus 13 weeks in placebo group) [19]. Like infliximab, adalimumab allows for a significant reduction in the mean corticosteroid dose and mean immunosuppression load required in noninfectious uveitis. Furthermore, adalimumab has been associated

with improvement in uveitic macular edema in prospective trials, which may be related to a reduction in plasma anti-VEGF levels with therapy [20].

Though less immunogenic than infliximab, adalimumab may still induce the formation of anti-drug antibodies in some patients, which may neutralize and limit the efficacy of the drug over time.

3.3.3 Safety

Overall, adalimumab is relatively safe for patients, and it is uncommon that the drug induces adverse events necessitating its discontinuation. Rates of lupus-like syndromes, and demyelinating disease and neuropathies, including optic neuritis, have been reportedly lower as compared to infliximab and etanercept. However, use of adalimumab still carries the risk of potentially devastating infections, including respiratory tract infections and reactivation of tuberculosis.

3.4 Golimumab

Golimumab (Simponi® and Simponi Aria®, Janssen Biotech, Inc., Horsham, PA, USA) was approved by the FDA in 2009 for the treatment of moderate to severe active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. Like adalimumab, golimumab is a fully human monoclonal antibody.

3.4.1 Administration

Golimumab is delivered either as monthly subcutaneous injections of 50 mg each month or as intravenous infusions. Similar to infliximab, the intravenous form of golimumab is loaded at 2 mg/kg at weeks 0 and 4 and then maintained with infusions every 8 weeks.

3.4.2 Efficacy

A limited number of case series describe success in treating cases of uveitis associated with ankylosing spondylitis, HLA-B27 positive status, juvenile idiopathic arthritis, and Behçet's disease after inadequate response to or intolerance of other TNF-α inhibitors [21, 22]. In a 2014 study by Miserocchi et al. of 17 affected patients, 14 patients experienced improvement in inflammation with golimumab therapy, with the majority achieving quiescence and corticosteroid-sparing effect over an average follow-up of 21.9 months [21]. Of note, the remaining three subjects were deemed non-responders.

3.4.3 Safety

Existing reports on the use of golimumab have not reported a significantly different rate of adverse events compared to that for other TNF inhibitors, though the evidence remains scant. Unlike the other TNF inhibitors, it has not been observed to cause a lupus-like syndrome.

3.5 Certolizumab pegol

Certolizumab pegol (Cimzia®, UCB, Inc., Smyrna, GA, USA) is approved for the treatment of moderate to severe rheumatoid arthritis, psoriatic arthritis, and Crohn's disease. Unlike fellow anti-TNF monoclonal antibodies, this agent is a polyethylene glycolated Fab fragment.

3.5.1 Administration

Certolizumab is initially administered as subcutaneous injections of 400 mg at weeks 0, 2, and 4, then continued as 400 mg injections monthly, or 200 mg injections every other week.

3.5.2 Efficacy

While certolizumab has shown efficacy in the management of systemic inflammation, limited data exist regarding its utility in uveitis at this time. A single retrospective case series of seven patients reports experience in the treatment of chronic immune-mediated uveitis (Behçet's disease, ankylosing spondylitis, psoriatic arthritis, and idiopathic retinal vasculitis) that had failed other TNF inhibitor therapy due to loss of efficacy or development of serious adverse effects. Over a mean follow-up period of 10.4 months, five of these seven patients developed quiescence with improvement in visual acuity and central macular thickness, with benefit seen as early as 1 month after initiation of certolizumab [23]. Another study reports decreased incidence of uveitis flares with certolizumab comparable to rates reported for other anti-TNF-α agents, but did not have sufficient numbers to establish statistical significance [24].

3.5.3 Safety

Existing reports on the use of certolizumab suggest risk for development of autoimmunity. It has been associated with a lupus-like syndrome, as well as bilateral panuveitis secondary to an ocular sarcoidosis-like reaction in a patient with rheumatoid arthritis and no prior history of sarcoidosis; signs and symptoms were noted to resolve following cessation of certolizumab in these cases [25, 26].

4. Adverse effects

4.1 Infections

TNF-α plays a crucial role in host immunity against infections, and correspondingly, blockade of TNF predisposes individuals to opportunistic infections, as well as reactivation of latent tuberculosis and hepatitis viruses. Patients on anti-TNF-α treatment also experience increased rates of invasive fungal infections, including histoplasmosis and coccidioidomycosis. Therefore, prior to initiating therapy, patients should be screened for active and latent tuberculosis with skin testing or an interferon gamma release assay, with a follow-up chest X-ray should these screening exams return positive. Patients who are diagnosed with tuberculosis should be treated for at least 1 month prior to initiating anti-TNF-α therapy. Hepatitis screening should also be performed before starting TNF inhibitors, with preceding hepatitis B vaccination for individuals not immune to hepatitis B, and concomitant prophylaxis against hepatitis virus reactivation during anti-TNF therapy for those with serologic evidence of hepatitis infection. Finally, pneumococcal and influenza vaccinations should also be considered. Once TNF-α inhibitors are started, live vaccines and unpasteurized milk should be avoided to reduce the risk of disseminated infection.

4.2 Malignancies

There is conflicting evidence in the literature regarding the risk of new as well as recurrence of prior malignancies with TNF-α therapy. Some registries have noted

an increased incidence of lymphoma and melanoma in these patients, and the FDA issued a black box warning in 2008 regarding potential association between use of TNF inhibitors and development of these cancers in children and young adults. Other studies report that TNF inhibitors may accelerate diagnosis of cancer in the first year of treatment, but may not increase long-term cancer risk [27]. Evidence for this may be confounded by the number of underlying conditions and history of other immunosuppressant therapy that patients carry. Regardless, patients being considered for TNF-α blockade should be informed of this potential risk.

4.3 Demyelinating disease and neuropathies

TNF inhibitors have been associated with central and peripheral neuropathies, including demyelinating and vasculitic neuropathies, and the pathogenesis for this phenomenon is unknown. A number of series have reported the development of Guillain-Barre syndrome and demyelinating lesions in the central nervous system similar to those in multiple sclerosis following initiation of anti-TNF-α therapy [28, 29]. For this reason, an MRI of the brain is recommended for patients with intermediate uveitis prior to starting TNF inhibitors to rule out underlying demyelinating disease, and these agents should not be prescribed to patients with evidence of demyelinating disease. If patients carry a positive family history, the risk of developing demyelinating disease should be discussed with them before proceeding with TNF-α blockers.

4.4 Congestive heart failure

Reports of atherosclerosis formation, promotion of plaque rupture, hypertrophy and heart failure from contractile myocardial dysfunction have been described with anti-TNF-α blockade. The New York Heart Association (NYHA) recommends against the use of TNF inhibitors in patients with NYHA class III or IV heart failure [30]. Those patients with compensated congestive heart failure (NYHA classes I or II) should undergo a baseline evaluation and be followed closely for any signs of worsening heart failure while on anti-TNF-α therapy.

4.5 Induction of autoimmunity

Anti-TNF-α agents may induce autoimmunity and formation of auto-antibodies, including antinuclear, anti-DNA, and anti-cardiolipin antibodies, among others. All of the TNF inhibitors, especially etanercept, have been associated with the onset of sarcoidosis [26, 31]. A rare lupus-like syndrome has been reported with all TNF antagonists with the exception of golimumab, and most commonly with etanercept and infliximab [32]. Other autoimmune diseases that have been reported include leukocytoclastic vasculitis, interstitial lung diseases, antiphospholipid syndrome-related features, autoimmune hepatitis and uveitis [31].

4.6 Endogenous uveitis

Paradoxically, there are reports associating TNF inhibitors with the onset or recurrence of uveitis, particularly with etanercept [33]. The mechanism is unclear, but one speculation is that as a soluble receptor, etanercept may prolong the half-life of TNF in the eye and potentiate uveitis if the receptor-ligand complex is not cleared promptly. Compared to infliximab, etanercept also has differential effects on T-lymphocytes and does not induce apoptosis. These differences may also contribute to observations of decreased efficacy of etanercept in certain inflammatory conditions [34].

4.7 Infusion reactions

The most common adverse effects of TNF inhibitor therapy are hypersensitivity reactions to the drug infusion, which are felt to be related to immune-complex formation and deposition. Most reactions are characterized by cutaneous, eczema-like eruptions at the site of injection, but may also include fever, nausea and vomiting, and arthralgia. These reactions may occur immediately after administration or in a delayed fashion up to 2 weeks after treatment. Of note, infliximab has been associated with a high rate of hypersensitivity reactions in up to 22% of patients undergoing infusion, and has been reported to cause angioedema and anaphylaxis [35]. Patients are hence often pre-medicated with Benadryl and acetaminophen to prevent these reactions.

4.8 Pregnancy

Pregnancy outcomes for women on infliximab have been reported through the Infliximab Safety Database and the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry, without evidence for an increased rate of miscarriages, birth complications, or fetal anomalies above that of the general pregnant population [36]. As an IgG antibody, infliximab does not cross the placenta during the first trimester, but readily crosses during the late second and third trimesters, and can subsequently persist in the infant for months after birth [37]. Therefore, based upon this and registry-reported outcomes, infliximab is generally considered safe during the first trimester and majority of the second trimester. However, it is advised that patients stop the drug during the late second or third trimester to minimize transfer to the fetus, and to avoid administering live vaccines to infants exposed to infliximab *in utero* given their increased risk for disseminated infection.

As a pegylated Fc-free agent, certolizumab does not cross the placenta in significant amounts, and is thus thought to be safer in pregnancy [38]. The largest published database on certolizumab use in pregnant women to date examined outcomes of 1137 prospectively reported pregnancies, without finding increased risk for teratogenic effects or fetal death as compared to the general population [38].

5. Monitoring clinical response

Once the decision has been made to proceed with TNF-α blockade, it is important to closely monitor patients for clinical response, as well as unwanted secondary effects. General routine clinical evaluation for infections, cytopenias, demyelinating disease, cancer, and cardiovascular alterations is essential, and may need to be performed in conjunction with a multidisciplinary team of specialists. Patient should also undergo serologic testing with a complete blood count and comprehensive metabolic profile every month for the first 3 months and at least every 2–4 months afterward. If testing results are abnormal, anti-TNF-α therapy should be deferred until these parameters have normalized.

The rate of nonresponse has been reported to be approximately 20% for patients initiated on infliximab therapy for uveitis [39]. Treatment response may depend on various factors, including age, location and severity of uveitis, and type of TNF-α blocker used. Genetic polymorphisms in TNF receptors and promoter regions may also impact the response to anti-TNF treatment.

Immunogenicity, in which an antigen induces an immune response after being recognized by a preexisting T-cell or B-cell receptor, may also occur and account for

suboptimal response or treatment failure. This may lead to drug trough levels that are lower than expected or the appearance of serum anti-drug antibodies, which lead to drug-antibody complex formation and consequent rapid clearance of the drug. Ocular and systemic inflammation may subsequently become resistant after several months of treatment. This phenomenon is most prevalent with infliximab, in which case these antibodies are referred to as human anti-chimeric antibodies (HACA), but also occurs with use of adalimumab.

Cordero-Coma and colleagues have summarized a proposal for patients not responsive or poorly responsive to anti-TNF therapy based on other studies [40]. If a patient is deemed to have insufficient clinical response to anti-TNF-α therapy, work-up of these patients with serum drug trough and anti-drug antibody levels may be warranted to guide management. High serum drug levels correlate with clinical response and decreased risk for relapse, and dosing should be individually optimized to attain a therapeutic drug level [41]. In patients with low drug trough levels, one should consider intensifying therapy by either increasing the dosage of each treatment or the frequency of dosing (up to every 4–6 weeks for infliximab and every week for adalimumab). If patients have suboptimal clinical response despite sufficient drug trough concentration, an alternative immunosuppressant with different mode of action may be required to control disease activity. Regardless of serum drug concentration, if anti-drug antibody levels are high, one should consider either switching to an alternative TNF inhibitor and/or adding concomitant steroids or other immunosuppression. Studies have shown that the traditional approach of intensifying therapy in antibody-positive patients is inferior to switching agents, with less treatment success and increased expense and risk of adverse effects [42].

There is not yet consensus regarding the preferred mode of assessing drug and antibody levels. Several assays are available, including enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, reporter gene assay, and homogeneous mobility shift assay, each with their own advantages and drawbacks. ELISA is the most readily accessible, but suffers from false-positive and false-negative results; the other modalities are more precise but logistically difficult to obtain [43].

6. Expert panel recommendations

In 2014, an Expert panel comprising a subcommittee of the American Uveitis Society published recommendations regarding the evidence-based use of anti-TNF-α agents [44]:

- Infliximab and adalimumab can be considered in preference to etanercept, which is associated with lower rates of treatment success.

- Infliximab and adalimumab can be considered first-line for treatment of ocular manifestations of Behçet's disease.

- Infliximab and adalimumab can be considered second-line for uveitis associated with juvenile arthritis.

- Infliximab and adalimumab can be considered potential second-line treatments for severe ocular inflammatory conditions, including posterior or panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients who have failed or are not candidates for antimetabolites or calcineurin inhibitors.

7. Conclusions and future directions

Tumor necrosis factor alpha inhibitors are mainstay treatments for several systemic immune-mediated conditions, including rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriatic arthritis, and serve as an important pillar of immunomodulatory therapy in the treatment of uveitis. Infliximab and adalimumab have both been shown to be successful at controlling ocular inflammation, particularly that related to Behçet's disease and juvenile arthritis. However, serious potential side effects, such as risk for opportunistic infections, reactivation of latent tuberculosis, and malignancy, may limit their use in uveitis. Further studies of the newer agents, golimumab and certolizumab, are warranted to establish their efficacy in uveitis, but early data regarding their safety have been promising, and they may represent future additional treatment options within this class.

Future directions for anti-TNF therapy include further studies of the significance of intravitreal formulations, as well as the development of biosimilars that may represent comparable and more affordable options to the traditional TNF antagonists. Intravitreal therapy with anti-TNF agents has been utilized and evaluated in very few studies with small sample sizes. The results have been variable and whether local therapy to the eye with these agents is safe and effective remains to be seen [45–48]. Biosimilars, defined by the World Health Organization as a biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product, provide potential economic alternatives to the current TNF-α agents. Despite the effectiveness and relatively rapid action of TNF inhibitors, the high cost may hinder accessibility to these drugs for some patients. A 2016 systematic review of 19 observational studies and clinical trials comparing biosimilar TNF-α inhibitors concluded that evidence supports the efficacy and safety of these agents [49]. The most notable existing biosimilar within this class is infliximab-dyyb, which exhibits similar qualities to the original product infliximab, and is currently available in many countries and was approved by the FDA in 2016. Several others are in development or already licensed for use outside the United States. As biosimilars become available, they may improve patient accessibility to these drugs for disabling disease.

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Conflict of interest

The authors have no conflicts of interest.

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