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Biologic Therapy For Ocular Inflammatory Diseases: An Update

Review Article

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Abstract

Uveitis comprehends a wide and heterogeneous group of intraocular inflammatory conditions potentially sight-threatening and variable therapeutic strategies have been proposed. Classical treatment with steroids and conventional immunosuppressive agents is often used as first-step. However, a number of patients may not respond properly or tolerate these medications with well-known side effects. Over the last two decades, advances in the understanding of the pathogenesis of autoimmune uveitis, as well as improved biotechnology, have enabled the development of a new class of drugs called biologics, which provide selective targeting of the immune mediators of the inflammation cascade. Biologic therapies were introduced as a new option for patients with autoimmune rheumatic conditions refractory to conventional therapy and due to their success have posteriorly been used in ophthalmology to treat ocular inflammatory disorders. These new agents may potentially provide more effective and less toxic treatment than conventional therapy. Biologic therapies include a wide variety of drugs with different mechanisms of action, including monoclonal antibodies against cell surface markers, cytokines and their receptors, or recombinant forms of natural inhibitory molecules. Although some results are based on investigations with insufficient clinical trials, the majority of biologics indicate preferable outcomes on refractory uveitis, with remarkable promise to increase the possibility of long-term remission. The development of these new drugs is one of the most revolutionary advances in recent years, and the promise of shifting paradigms makes it an exciting time for uveitis specialists worldwide.

Keywords: Uveitis; Ocular Inflammation; Biologics; Cytokines; Immunomodulation

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Introduction

Uveitis is a major cause of severe visual impairment that accounts for 10–15% of all cases of total blindness in the US, and one of the major causes of visual handicap within the working population worldwide[1]. The pathogenesis of ocular inflammation is believed to involve an abnormal T-cell response to ocular antigens, which leads to T-cell–mediated damage to the eye [2]. Augmented levels of inflammatory cytokines, specifically tumor necrosis factor-α (TNF-α) have been implicated in the pathogenesis of various ocular inflammatory diseases. Suppressing the immune response with steroids or with conventional immunosuppressive drugs forms the mainstay of treatment [3]. This achieves disease control and prevents vision-threatening complications in most patients, but a significant proportion of patients remain unresponsive to conventional immunosuppression and with diminished quality of life [2]. Over the last two decades, advances in the understanding of the pathogenesis of autoimmune uveitis, as well as improved biotechnology, have enabled the development of a new class of drugs called biologics, which provide selective targeting of the immune mediators of the inflammation cascade. These drugs may potentially provide more effective and less toxic treatment than conventional immunosuppressive agents. Biologics include a wide variety of drugs with different mechanisms of action, including monoclonal antibodies against cell surface markers, cytokines and their receptors, or recombinant forms of natural inhibitory molecules. This article summarizes the principal biological agents used for the treatment of noninfectious uveitis. The development of these new drugs is one of the most revolutionary advances in recent years, and the promise of shifting paradigms makes it an exciting time for uveitis specialists worldwide.

Tumor Necrosis Factor Alpha (TNF-α) Antagonists

TNF-α is a pleiotropic cytokine expressed in a wide variety of inflammatory conditions contributing to the pathogenesis and perpetuation of autoimmune disease. It is produced by different cell types and mediates its effect through two receptors, p55 (TNFR1) and p75 (TNFR2) [4]. During inflammation TNF-α activates T cells and macrophages and upregulates other proinflammatory cytokines. Experimental models of uveitis have provided substantial evidence of TNF-α's pivotal role in mediating intraocular inflammation [5,6]. 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 [7-10]. In late 1990s Dick et al. demonstrated the benefits of TNF-α inhibition in minimising the severity of experimental autoimmune uveoretinitis [11]. Neutralizing TNF-α activity results in skewed T-cell polarization with reduced IFNα generation, suppressed levels of T-cell apoptosis, and reduced levels of classical myeloid cell activation, resulting in suppressing target organ damage [5,11]. There are currently 5 TNF antagonists approved for use in rheumatic diseases. 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 (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-α, thereby resulting in decreased expression of adhesion molecules responsible for leukocyte migration and reduced synthesis of proinflammatory cytokines[12]. It is administered subcutaneously at a dose of 25-50 mg twice a week. Etanercept has been effective in the treatment of several rheumatic diseases [12,13], although its effect in uveitis is debatable [14,15]. Foster et al. showed that etanercept has no significant efficacy over placebo in preventing relapses of uveitis[14]. Moreover, etanercept can worsen uveitis course or even induce ocular inflammation in a paradoxical effect [16-19].

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[20]. An alternative inhibition mechanism of infliximab is the promotion of regulatory T (Treg) cells that acquire suppressive functions in the periphery [21]. 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 a 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, psoriasic 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, sympathethic ophthalmia) [22-27], but most of the evidence of the effectiveness of infliximab in ocular inflammatory disease comes from studies on its use in Behcet´s disease [28-34]. 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 [28,29]. Recently, Japanese investigators have conducted a multicenter prospective study [31] 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 methilprednisolone [34]. 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 [32,35,36]. Infliximab is also efficacious in extraocular manifestations of Behçet's disease such as oral and genital ulcers and /or arthritis in the majority of patients.

Recent reports have suggested the possibility of intravitreal use of infliximab [37,38]. 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 SITE cohort study showed that patients on anti-TNF therapies have a greater risk of cancer and overall mortality [39]. 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 [40].

The remaining targeting antibodies are all given through subcutaneous injections.

Adalimumab (Humira®, Abbott, Chicago, IL, USA) is a fully humanized monoclonal antibody that inhibits TNF-α. It is administered in subcutaneous injections40 mg every 2 weeks. When uveitis relapses still occur despite this dose, adalimumab may be administered weekly until achieving control of inflammation [41]. 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 [42-45]. Recently, Diaz-Llopis et al. conducted a prospective study of 131 patients with refractory uveitis treated with adalimumab [46]. 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.

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

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 [47]. 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 [47]. 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 [48-50], 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 (Cimzia®) consists only in the pegilated 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 [51]. Certolizumab has been approved for in Crohn's disease and rheumatoid arthritis in people who did not respond to standard therapy [52]. 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 noninfectious uveitis.

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 [53,54].

Interferons

Interferons (IFN) are a group of cytokines that include type I IFN (IFNα and IFNα, produced mainly by antigen-presenting cells) and type II (IFNα), produced by T cells and NK cells. IFNs, are thought to have an important role linking the innate with the adaptive immune system [55]. IFN-α has immunoregulatory and mmunosuppressive effects [56] and has been shown to be beneficial in the treatment of patients with uveitis [57-59]. Currently there are two types of different human recombinant IFNα that are commercially available: non-pegylated and pegylated. The first class includes IFN-α2a (Roferon-A®) and IFNα-2b (IntronA®). Pegylated ones are Peginterferon-α2a (Pegasys®) and IFNα-2b (ViraferonPeg®). Pegylation increases the size and the half-life of the molecule to obtain higher serum concentrations. IFNα is approved for the treatment of viral hepatitis C and B. IFNα is given by subcutaneous injections. There is no consensus about the ideal dose and duration of the treatment. It is usually started with high-dose daily injections 3 $x10^6$ to 9 x 10^6 IU per day, with a subsequent taper to low dose intermittent injections (3 x 10^6 IU two or three times a week) [56]. Steroids and immunosuppressive drugs may antagonize the effect of IFNα, so the standard procedure includes discontinuation of immunosuppressive medications prior to start IFNα therapy or reduce its doses as much as possible. IFNα was the first biological agent used for the treatment of Behçet's disease before the advent of TNF antagonists. Due to its antiviral effect, IFNα was first used in the middle 1980s in Behçet patients who were refractory or intolerant to conventional treatments, given the fact that one of the pathogenic hypothesis of Behçet's disease states that it may be triggered by a viral infection [59]. Kötter et al. reviewed 338 BD patients treated with IFNα, 182 of them for acute uveitis [60]. This study showed that about 94% of the patients reached complete remission (disappearance of all symptoms) or at least partial remission (a >50% decrease in number, severity, duration or frequency of lesions or scores) of ocular Behçet's disease within 2-4 weeks. In addition, IFNα may lead to stable remission after discontinuation of treatment. In Behçet patients, after a mean treatment duration of 15 months, long-term remission could be maintained in 56% of patients after discontinuation of IFNα therapy [61]. Outside ocular BD, IFNα has proved to be an effective treatment for other uveitis such as sympathetic ophthalmia, Vogt-Koyanagi-Harada disease, Birdshot retinochoroidopathy, and serpiginous choroiditis[56,58]. Recently, Butler et al evaluated the efficacy of IFN-α2b in the treatment of refractory, uveitic cystoid macular edema in 4 patients who failed therapy with locally injected corticosteroids, and found that treatment with systemic IFN-α2b produced dramatic improvement in central macular thickness and visual acuity [62] Another potential advantage of IFN-αtherapy is that, unlike other immunosuppressants and biologics, does not increase the risk of opportunistic infections and is not carcinogenic. However, side effects are almost universal and some of them can be fairly dangerous, becoming the main limiting factors of IFNα use [63]. Flu-like syndrome, consisting of fever, fatigue and headache occur in 100% of patients during the first weeks of therapy, although rarely are severe enough to discontinue therapy. Other serious side effects include hematological toxicity, alopecia, elevated liver enzymes, bowel dysfunction, and injection site ulcers. Psychiatric disorders such as depression, anxiety, and psychoses, reported in 4 to 7.5% of patients, can lead to suicide and thus are limiting

factors for the use of IFN [63]. Development of systemic autoimmune diseases such as sarcoidosis or lupus induced by IFN has also been reported [63].

IL-1β Antagonists

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine secreted by a wide variety of cell types. It is a key initiator and mediator of the inflammatory cascade and a pivotal cytokine in the inflammasome: IL-1β acts as a messenger to upregulate the innate immune system's response to infection, injury, and stress [64]. IL-1β exerts its effects through interleukin-1 receptor type I (IL-1RI) and interleukin-1 receptor accessory protein (IL-1RAcP), which together form a heterotrimeric signaling-competent complex. IL-1β signalling induces cells to express additional cytokines (including IL-1β) as well as chemokines and other pro-inflammatory molecules. Elevated levels of IL-1β play a major role in many autoinflammatory and autoimmune diseases [64]. For instance, Behçet's disease has many clinical findings overlapping with those of autoinflammatory disorders, and circulating monocytes of patients with Behçet's produce large amounts of IL-1β [65].

Targeting IL-1 began in 1993 with the introduction of Anakinra (Kineret®), a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra), which blocks the activity of both IL-1α and IL-1β. It is administered with an adult dose of 100 mg daily by subcutaneous injection. It has been used to treat a wide variety of autoinflammatory conditions, including chronic infantile neurological cutaneous articular syndrome (CINCA)-associated uveitis refractory to anti-TNF therapy, confirming the success in the preclinical experimental autoimmune uveitis model in mice [66]. Serious infections such as pneumonia and infectious cellulitis seem more frequent with anakinra, although there is no increased risk of tuberculosis.

Canakinumab (ACZ885) is a novel fully human IL-1β blocking antibody. It binds IL-1β, inhibiting its binding to IL-1 receptors I and II. Intravenously or subcutaneously infused, it neutralizes the bioactivity of human IL-1β, which is involved in several inflammatory disorders [67]. Canakinumab has promising clinical safety and pharmacokinetic properties, and demonstrated potential for the treatment of cryopyrin-associated periodic syndromes (CAPS) and possibly for other complex inflammatory diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, and ocular inflammatory diseases [68,69]. Early clinical trials have established the administration of canakinumab every 2 weeks to be safe and effective, offering a considerable advantage over anakinra, which must be injected daily and is often poorly tolerated by patients. Two recent reports showed the efficacy of canakinumab in Behçet's uveitis refractory to TNF antagonists[70,71].

Gevokizumab (XOMA 052) is a recombinant, partially humanized monoclonal antibody that binds IL-1β, reduces affinity to IL-1RI, leaving intact the affinity for IL-RII. It is a modulating antibody that does not block the assembly of IL-1β signalling complex. It down-regulates IL-1β activity in cytokine release assays. It has a circulating half-life of approximately 25 days, allowing once monthly dosing [72]. Gül et al. have recently conducted an open-label pilot study to evaluate safety, clinical/biological activity and pharmacokinetics of gevokizumab in 7 BD patients with acute intraocular inflammation resistant to immunosuppressive treatment[73]. Gevokizumab 0.3 mg/kg was administered in a unique intravenous injection in all patients at day 0, followed by a second infusion in 5 patients who relapsed between days 49 and 95 of the study. Immunosuppressive therapies were suspended before entering the study. Relapses occurred when drug serum level felt below 2 μg/ml. Following the second infusion all patients remained attack free without the need for any other medication for a median of 115 days. The authors reported no treatment-related adverse events. Limitations of this study include its open-label design, the small number of patients, the lack of assessments of the extraocular manifestations, and the short follow-up. There are two ongoing phase III clinical trials studying the safety and efficacy of gevokizumab in noninfectious uveitis (Eyeguard™-A and –C) which are currently recruiting.

IL-2 Receptor Antagonism

IL-2 is an essential cytokine in the activation of T-lymphocytes. The IL-2 receptor (IL2R) system plays a central role in the induction of immune responses via activated T and B-lymphocytes, observed both in uveitis animal models and on the surface of human cells in patients with uveitis. Daclizumab (Zenapax®) is a humanized monoclonal antibody directed against the CD25 subunit of the IL2R, which is present on activated T cells. It was first approved by the FDA in 1997 for the prevention of allograft rejection [74]. Daclizumab has demonstrated promise in the treatment of childhood uveitis [75] and non- infectious intermediate and posterior uveitis [76,77], being particularly effective for Birdshot retinochroidopathy. Typically it is dosed 1-4mg/kg intravenously every 2 weeks. Unfortunately, its manufacturer withdrew this promising medication from the market in January 2010.

IL-6 Receptor Antagonism

Tocilizumab (Actemra®) is a humanized monoclonal antibody that blocks the IL-6 receptor. IL-6 is a pleiotropic, proinflammatory cytokine mainly produced by T cells and monocytes/macrophages, inducing proliferation and differentiation of T cells as well as the terminal differentiation of B cells. Serum levels of IL-6 are significantly elevated in patients with active noninfectious uveitis and decrease during remission [78,79]. In addition, elevated intraocular levels of IL-6 were observed in patients with active intermediate or posterior uveitis and probably play an import role in uveitis and macular edema pathogenesis[80,81]. Tocilizumab is approved for the treatment of rheumatoid arthritis and is dosed 4-8mg/kg, given in intravenous infusion every 4 weeks. The effectiveness of tocilizumab in uveitis has been reported in a few small case series so far. Muselier et al. found tocilizumab to be effective in two refractory uveitis cases[82]. Tappeiner reported 3 patients with refractory uveitis associated with juvenile idiopathic arthritis[83]. Effectiveness of tocilizumab treatment in Behçet's uveitis has also been reported [84]. Our group recently reported two papers studying the efficacy of tocilizumab infusions in uveitis cases with severe cystoid macular edema refractory to systemic and local treatments [85,86]. It is usually very well tolerated and has a good safety profile. Given that IL-6 blockade does not affect granulomatous inflammation, tuberculosis does not pose a safety issue. There are currently 3 ongoing clinical trials to study the efficacy of tocilizumab in patients with non-infectious uveitis (the STOP-uveitis study, NCT01717170), juvenile idiopathic arthritis associated uveitis (NCT01603355), and Behçet's syndrome (NCT01693653).

Anti-CD20

Although much attention gets focused to the cellular arm of the adaptive immune system, the humoral arm certainly plays a role in many autoimmune diseases. Rituximab is a chimeric monoclonal antibody that binds specifically to the B lymphocyte antigenCD20 –present only in mature B cells-, inducing B cell death by apoptosis. Rituximab (Mabthera®/Rituxan®) was a revolution in the treatment of B-cell lymphoma and has shown efficacy in many autoimmune diseases with circulating autoantibodies such as rheumatoid arthritis, systemic lupus erythematosus, Wegener's and anti-neutrophil cytoplasmic antibody-associated vasculitis [86,87]. With respect to ocular disease, it is especially useful in masquerade syndrome due to intraocular lymphomas [88]. Rituximab has also been used to treat ocular cicatricial pemphigoid, noninfectious scleritis, peripheral ulcerative keratitis [89], and several cases of refractory uveitis [90]. Rituximab is given intravenously 375mg/m2 surface area usually every 2 weeks. Previous intravenous administration of corticosteroids is recommended to prevent allergic reactions. Side effects may appear during the first infusion, such as fever, rash, respiratory symptoms and hypertension. Increased risk of severe infections is one of its major safety issues. The administration of rituximab is followed by a transient depletion of CD20 positive B cells that may last 6-9 months, therefore B cell counts should be monitored.

T-Cell Co-Stimulation Inhibition

Abatacept (Orencia®) is a fusion protein formed by a ligand-binding domain of the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and a fragment of human immunoglobulin. It induces a blockade of the interaction between the T-cell co-stimulatory receptor CD28 and CD80/CD86 expressed on antigen presenting cells, thus inhibiting the co-stimulation and the activation of T lymphocytes [91]. It is approved for the treatment of refractory rheumatoid arthritis. There is emerging data demonstrating efficacy in the setting of recalcitrant Juvenile Idiopathic Arthritis- associated uveitis that has failed traditional immune modulation or TNF Inhibitors [92]. It is administered with a 30-minutes slow intravenous infusion, given every 2 weeks for the first 3 doses and then every 4 weeks. It is dosed according to the weight of the patient: 500 mg for patient weight<60kg, 750mg for patient weight 60-100kg, 1000 mg for patient weight>100kg. Subcutaneous abatacept formulation is now available in some countries, with a similar long-term efficacy to the intravenous formulation and a lower immunogenicity [93]. The most relevant but infrequent adverse events related to abatacept are pneumonia, lymphoma and breast cancer. It is currently under investigation in phase II trials for the treatment of uveitis (NCT01279954).

Other Emerging Therapies

Fingolimod (FTY720) is a sphingosine-1-phosphate receptor modulator and the first an FDA-approved oral drug for the treatment of multiple sclerosis. Fingolimod prevents T-cell migration to inflammatory sites by decreasing expression of the sphingosine-1 phosphate receptor normally required for egress from secondary lymphoid tissue. In murine models, fingolimod reduces ocular infiltration within hours of administration and suppresses clinicopathologic expression of experimental autoimmune uveoretinitis [94]. These results support a strong therapeutic potential for fingolimod as a treatment of ocular immune-mediated inflammation and may be an effective agent for an acute rescue therapy for sight-threatening intraocular inflammation [95]. Two recent clinical trials (TRANSFORMS and FREEDOMS) demonstrated a significant reduction in the relapse rate of patients with multiple scleroses when compared to interferon beta and placebo [95]. However, macular edema was a prominent adverse event, observed in 0.5% of patients treated with fingolimod. A recent study conducted by Zarbin et al. observed 19 cases with macular edema among 2615 patients receiving fingolimod for multiple sclerosis [95]. Fingolimod-associated macular edema tends to appear within 3-4 months of treatment initiation and it is more prevalent in patients with a history of uveitis. In most cases, macular edema resolves after discontinuing the drug [95]. There is currently a phase II clinical trial to study the safety, tolerability, and efficacy of FTY720 in patients with noninfectious uveitis (NCT01791192) sponsored by Novartis.

Secukinumab is a fully human monoclonal antibody for targeted IL-17A, which is recognized as one of the principal proinflammatory cytokines in immune-mediated inflammatory diseases. Higher levels of IL-17A have been found in the peripheral blood of patients with uveitis and other systemic immune-mediated conditions, such as Vogt–Koyanagi–Harada syndrome and Behçet's disease, compared with healthy controls or affected patients with quiescent uveitis [96]. In 2007, Amadi-Obi et al reported substantial elevation in IL-17A expression in the serum of patients with active uveitis and in animal models of uveitis and demonstrated that IL-17A inhibition suppresses disease activity [97]. Dick et al. recently reported the findings from 3 clinical trials designed to explore the efficacy and safety of different doses of secukinumab versus placebo in the treatment of noninfectious uveitis [98]. The trials enrolled patients with Behçet's disease with posterior uveitis or panuveitis (SHIELD study); patients without Behçet's disease with active, noninfectious uveitis (INSURE study); and patients without Behçet's disease with quiescent, noninfectious uveitis (ENDURE study). After completion of the SHIELD trial, which showed insufficient evidence for the efficacy of secukinumab, a decision was made to terminate the INSURE trial early. The ENDURE trial also was terminated early because the results of a prespecified interim data analysis did not show sufficient evidence of efficacy. However, the observed effects of secukinumab on several clinical parameters may provide insights into uveitis pathophysiology that could be useful for guiding future approaches to treatment.

Discussion

Targeted immune modulators work by selectively blocking mechanisms involved in the inflammatory and immune response. The advancement of our understanding immunologic mechanisms behind autoimmune and in particular ocular inflammatory diseases has begun to yield many new and diverse therapies that hold great promise for immune modulation in the years to come. Among the studies quoted in this paper in support or against a particular drug, most are retrospective reviews, small studies that have no standard definition of success. In addition there is also a strong heterogeneity of the study variables. Another limitation is the variability of the uveitis etiologies among the patients included in most of the studies. The first and foremost issue is how do biologics really work in uveitis? For example, peripheral monocytes taken from patients with active ocular Behcet's disease are known to produce greater amounts of TNF-α compared with patients with Behcet's disease and quiescent eyes or normal controls. There is evidence to support the role of TNF-α as a central proinflammatory cytokine contributing to the inflammatory cascade that ultimately leads to tissue destruction in uveitis.

Unfortunately, the biological basis for therapy is less certain with other drugs. Furthermore, although biologic agents being used in patients with uveitis have first been tested in rheumatologic disease, not all agents that are effective in systemic disease are effective in the eye. As we previously mentioned, etanercept works well in rheumatoid arthritis but has less efficacy in uveitis and has even been reported to trigger de novo ocular inflammation in some patients being treated for their systemic disease. The reasons for differential efficacy between organs are poorly understood.

We considerer 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.

An important issue regarding the use of TNF inhibitors is if this therapy could be discontinued at any time in those patients achieving control of their uveitis. Some included studies reflect that this option may be possible, although most of the patients in these studies were on immunomodulatory drugs at the time in which anti-TNF therapy was discontinued. The measurement of serum levels of TNF antagonists and /or antibodies against these agents, which may explain a possible tachyphilactic phenomenon, seem to be a reasonable work-up in the future management of patients treated with TNF antagonists. These rates of adverse events are higher than those reported in shorter-term retrospective studies. Clearly, there are real related to biologic therapies about which both the physician and the patient need to be fully informed. Moreover, because of the high cost of biologic agents, whether we can actually use them unfortunately does not only depend on good evidence. The use of new and expensive medical therapies such as biologics is increasingly being controlled by health insurance corporations and healthcare regulatory agencies. Although options are many and diverse, further interventional and longitudinal studies must be done to clarify which medications impact which diseases. Due to the chronicity of most noninfectious uveitis and the unpredictability of remissions and exacerbations of the inflammatory reactions, there is a need for masked evaluations, with long follow-up data, and larger numbers of patients for adequate and unbiased testing of the available novel biologic drugs.

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