Chapter

Biological Therapies that Target Inflammatory Cytokines to Treat Uveitis

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Abstract

Uveitis is a leading cause of blindness that presents a considerable challenge given that our understanding of the mechanisms of disease is still evolving. Both innate and adaptive immunity play a role in disease and mediators of these responses can serve as therapeutic targets. TNF-α and IL-1β inflammatory cytokines are central mediators of immunity and are involved in the dysregulated inflammatory response during uveitis. Because toxicity limits the use of steroids and other steroid-sparing agents, biologics that target a specific cell type or pathway are being explored for the treatment of autoimmune uveitis. This chapter begins with a broad overview of the aberrant immune response resulting in uveitis, and highlights key mediators such as TNF-α, IL-1β, IL-6, and IL-17 and their potential use as therapeutic targets. Most biological agents discussed in this review have not been FDA-approved for uveitis. However, favorable outcomes in early trials and FDA approval of these drugs for the treatment of other autoimmune diseases associated with uveitis support the potential for these biological agents in the management of uveitis. This review aims to provide an updated report on the efficacy of biologics that target TNF-α, IL-1β, IL-6, and IL-17 for the treatment of autoimmune uveitis.

Keywords: uveitis, TNF-α, IL-1β, IL-6, IL-17, etanercept, adalimumab, infliximab, golimumab, certolizumab, anakinra, canakinumab, gevokizumab, rilonacept, tocilizumab, sarilumab, secukinumab

1. Introduction

Uveitis is the third leading cause of blindness in western countries and fourth worldwide [1, 2]. The ocular inflammation associated with uveitis can occur in every tissue within the eye so is frequently described according to the anatomical location of the inflammation [3, 4]. Anterior uveitis includes inflammation of the iris, ciliary body, and anterior chamber. Intermediate uveitis involves the vitreous and pars plana, while posterior uveitis describes inflammation of the retina and choroid [5, 6]. Sometimes, both anterior or intermediate and posterior uveitides can occur, which is referred to as panuveitis [5, 6]. Uveitis can be due to infectious or noninfectious causes; the latter is thought to be immune mediated and is commonly referred to as autoimmune uveitis (AU) [7, 8]. Both infectious and noninfectious uveitides lead to damaging inflammation, and undertreatment leads to destruction of ocular tissue which can result in vision loss [9, 10]. So, the goal of treatment is

to suppress the ocular inflammation to preserve vision [7]. Generally, uveitis of infectious origin is treated with systemic and/or local antibiotics, antivirals, or antifungals, and inflammation usually resolves once the pathogen is eliminated [7]. Because noninfectious uveitis is immune-mediated, suppression of the immune system is necessary [7, 11].

The current treatment paradigm for noninfectious uveitis is to treat with medications that suppress the immune system to drive the inflammatory response into remission [2, 7]. Corticosteroids can be given locally and/or systemically to rapidly suppress inflammation, but they are not a long-term treatment option due to their side effects [7, 12–14]. When the steroids are discontinued, there is a risk of recurrent disease [15]. Localized slow-releasing steroid implants have been developed and have shown some efficacy, but these can result in cataract and glaucoma [14, 16]. As such, immunomodulating or immunosuppressants are used concomitantly to supplement or taper off the steroids in severe or chronic cases [7]. These immunosuppressive therapies, also called "steroid-sparing drugs," include nonsteroidal anti-inflammatory drugs (NSAIDs); antimetabolites such as methotrexate, azathioprine, and mycophenolate; T-cell inhibitors such as tacrolimus; and cyclosporine and mTOR inhibitors such as rapamycin and derivatives of rapamycin [2, 7]. Also, DNA alkylating agents such as chlorambucil and cyclophosphamide can also be utilized. The steroid-sparing drugs have significantly improved the outcome of uveitis and provide additional more targeted treatment options [17]. However, as with steroids, these drugs may produce significant side effects, including an increased susceptibility to infection, and many still fail to provide lasting remission [2, 18]. It is conceivable that a targeted therapy that only suppresses one or two inflammatory pathways may offer a more favorable side effect profile than standard steroid-sparing agents [2]. Biologics are a relatively new class of medications that specifically target specific molecules involved in inflammation. The major hurdles to implement biological therapies include a large financial burden and questions about long-term efficacy. Therefore, in this report we discuss the outcomes of treating uveitis with biologics with a specific focus on inhibition of TNF-α, IL-1β, IL-6, and IL-17 inflammatory cytokines.

1.1 Biologics in uveitis

Progress in the field of ocular immunology has provided a basic understanding of the inflammatory mechanisms that contribute to the pathogenesis of noninfectious uveitis. This allows for a better understanding of the mechanism of action of many medications. Many of the current immunosuppressive therapies suppress inflammation via broad mechanisms of action. For example, mycophenolate inhibits expansion and survival of lymphocytes by limiting the transport of purines into the cell, thus preventing proliferation of T cells and B cells which are dependent on extracellular purines [19]. The disadvantage of this strategy is that differentiation of regulatory T cells (Tregs), a subset of T cells, that have been demonstrated to suppress autoimmune disease would also be inhibited [20, 21]. Rapamycin inhibition of mTOR is effective in suppressing rapidly dividing cells such as leukocytes, but the mTOR pathway is utilized by many cells in the body, so mTOR inhibitors are associated with a wide array of side effects [22]. Therefore, the effective treatment of autoimmune uveitis with a minimal side effect is dependent on the development of much more targeted treatments.

A better understanding of autoimmune diseases and specifically of ocular immunology now provides the possibility of specifically targeting important inflammatory pathways rather than broadly suppressing the immune response [14]. One such method to target specific inflammatory cytokines or receptors is with the

use of biologics [2, 14, 23]. The biological agents, also called "biological response modifiers" or "biologics," are a broad group of molecules that have been utilized to interfere and alter inflammation during immune-mediated processes [2]. These agents include recombinant cytokines, monoclonal antibodies that target cell surface proteins and receptors, specific antagonists of cytokines, and soluble receptors [14, 24]. These drugs function by specifically suppressing a single pathway through targeting of an effector molecule [14, 23]. As such, biological agents are being used as a treatment for refractory uveitis [25, 26]. Unfortunately, biologics are not always an option because of extremely high costs that limit approval for off-label use by insurance. The justification to insurance can be even more challenging because of the limited number of published reports documenting the effectiveness of biologics. As such, it is necessary to demonstrate that current biologics are effective in providing sustained remission. Therefore, the purpose of this review is to provide a summary of the literature of the outcomes and effectiveness of biologics that target the key inflammatory mediators especially TNF-α, IL-1β, IL-6, and IL-17. In addition, in order to provide a better understanding of the immunological function of these biologics, we will also provide a limited discussion of the immunological pathways that are targeted by TNF-α, IL-1β, IL-6, and IL-17.

1.2 Basic immunology of uveitis

Immune-mediated or autoimmune uveitis is a group of heterogeneous diseases that can be restricted to the eye, as in pars planitis or birdshot chorioretinopathy. The vast majority of uveitis patients experience localized inflammation. However, ocular inflammation can also be associated with systemic disease, such as in lupus, ankylosing spondylitis, and multiple sclerosis [27]. There are still many unknown aspects of the pathogenesis of autoimmune uveitis, but results from human and animal research supported potential mechanisms. One theory is the molecular mimicry model, in which the manifestation of autoimmune uveitis is thought to result from clearance of a pathogen with an antigen with a similar structure to a self-antigen in the eye [28–30]. However, the initiating antigens have not been isolated nor is it likely to be identified due to antigenic shift that occurs with chronic tissue inflammation [31]. In some cases, there is a genetic component, as evidenced with gene associations mapping to the HLA locus, such as HLA-B27, HLA-A29, and HLA-B51 [32–34]. HLA-B27 is associated with anterior uveitis, reactive/rheumatoid arthritis, and ankylosing spondylitis. HLA-A29 is associated with birdshot chorioretinopathy, and HLA-B51 is associated with Behcet's disease [35–37]. Because there is not 100% penetrance with these HLA alleles, there is likely also an environmental trigger that is required as well. This demonstrates the heterogeneity associated with autoimmune uveitis and illustrates why a single therapy may not be effective for all uveitis patients. Thus, additional research is necessary to further our understanding of this disease.

Innate and adaptive immune cells are intricately connected during a normal immune response and aberrant responses as in autoimmune uveitis [30, 38]. The trigger of immune activation during uveitis is not well understood, but it is speculated that both environmental and genetic predispositions can initiate an inflammatory response that would eventually cause damage to the eye during uveitis [39, 40]. Innate immune cells such as monocytes, macrophages, and dendritic cells generally respond first to these inflammatory cues [41, 42]. These activated innate immune cells secrete proinflammatory cytokines such as TNF-α, IL-6, and IL-1β which serve as mediators of inflammation [34, 38, 43]. The role of innate immunity in the pathogenesis of uveitis is evident in both human and animal studies, where

markers of inflammatory monocytes are more abundant in uveitis patients than their healthy controls [44]. Likewise, high levels of these inflammatory cytokines have been shown to be elevated in the ocular fluids of uveitis patients [45]. Also, animal models of uveitis which recapitulate the pathologies seen in human uveitis require adjuvants in the induction of the T-cell-mediated uveitis [46]. These required adjuvants activate the pattern recognition receptors (PRR) on innate immune cells that result in the production of these TNF-α, IL-1β, and IL-6 [34, 38]. As such, inhibition of TNF-α, IL-1β, and IL-6 is effective in reducing the ocular inflammation observed in numerous mouse models of uveitis [47–49]. Activated innate immune cells can act as antigen-presenting cells (APCs) and/or cytokine-secreting cells to provide signals that activate B and T cells [50]. In response to this activation, T cells differentiate into effector cells and largely produce inflammatory mediators such as cytokines that activate and recruit other immune cells that enhance ocular damage [34].

Several studies have highlighted the involvement of mediators and cellular responses that integrate both innate and adaptive immunities in the pathogenesis of uveitis [30, 41]. In this review, TNF-α, IL-17, IL-6, and IL-1β are the mediators of interest. While TNF-α, IL-6, and IL-1β are central mediators of inflammation that lead to activation of both innate and adaptive immunities, IL-17 is produced by a specific effector T cells (Th17 cells) that has a strong association with autoimmunity [51, 52]. Elevated levels of these cytokines are seen in the ocular fluids and plasma of uveitis patients [53–55].

Biological agents that specifically target these immune mediators or T-cell-activating molecules have gained wide recognition as effective therapy for immune-mediated diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriasis, sarcoidosis, and organ rejection and are therefore being used for the treatment of uveitis [56]. Results from treatment of animal models and biological samples of uveitis patients with antagonists of the inflammatory mediators have demonstrated the involvement of these mediators with autoimmune uveitis [57, 58]. Currently, there are numerous clinical trials that are testing the efficacies of biological agents for the treatment of autoimmune uveitis.

2. TNF-α inhibitors

TNF-α inhibitors are biological agents that target tumor necrosis factor alpha (TNF-α) and its receptors. TNF-α was initially studied for its ability to stimulate necrosis of malignant tumors [59, 60]. An immunological role was later discovered as it is also an important inflammatory mediator [59, 60]. TNF-α is a proinflammatory cytokine that is secreted by many immune cells of the innate and adaptive arm of the immune response, including T cells, and macrophages, and nonimmune cells such as keratinocytes [60]. TNF-α binding to one of the two isoforms of its transmembrane receptor (TNFr1 and TNFr2) is the first step in triggering a response [59]. Binding of TNF ligand to its receptor activates downstream signals that lead to a cascade of cellular events that include cellular proliferation, differentiation, apoptosis, survival, and regulation of inflammatory cytokine production [60]. Because these events lead to activation of inflammatory cells, TNF-α is considered a master regulator of inflammation [60, 61]. TNF-α has been implicated in the pathogenesis of autoimmune uveitis and other immune-mediated diseases especially organ-specific diseases [62–64]. High levels of TNF-α have been reported in the aqueous humor and sera of uveitis patients compared to their healthy controls [65]. Also, elevated levels of this cytokine are observed in

the animal models of autoimmune uveitis, and inhibition of TNF-α activity results in disease remission in these animal models [47, 66]. Involvement of TNF-α in many autoimmune diseases has made it a therapeutic target [60]. Currently, there are numerous biologics that target TNF-α activity; these include infliximab, etanercept, adalimumab, golimumab, and certolizumab [67]. Biologics that target TNF-α and its interaction with its receptors were developed and approved for the treatment of autoimmune diseases such as RA, psoriasis, sarcoidosis, inflammatory bowel disease, etc. [67]. The efficacy of TNF-α inhibitors in the treatment of these diseases has led to great interest in the use of these biological agents for the treatment of uveitis.

2.1 Etanercept

Etanercept is a recombinant fusion protein that contains the extracellular ligand-binding portion of the human TNF receptor (TNFr2) and the Fc portion of human IgG1 [68]. Because the structure of etanercept contains no membrane-bound portion, it is essentially a soluble TNF receptor that binds the free form of all TNF isoforms (TNF-α, TNF-β, and TNF-γ) [68]. Because the soluble form of TNF and membrane-bound TNF have opposing immunological effects, it is of note that etanercept does not bind to the membrane-bound form [69].

For two decades, etanercept has been used to treat rheumatic diseases, and it is FDA approved for the treatment of JIA, RA, ankylosing spondylitis (AS), psoriatic arthritis (PA), and plaque psoriasis (PP) [68, 70]. Effectiveness of etanercept in the treatment of these diseases led to interest in the use of this drug for uveitis. Etanercept has been reported to be a treatment for refractory uveitis in pediatric patients [71]. In the prospective study, beneficial effects of etanercept were observed in at least 63% of the patients after 3 months of treatment [71]. Another prospective study of the efficacy of etanercept in patients with JIA-associated uveitis showed 73% of the patients had an initial response after 3 months of treatment; however, only about half of the responders (39%) remained in remission after 1 year [72]. In addition, several prospective and retrospective studies of etanercept did not show treatment efficacy in uveitis associated with systemic diseases such as JIA [73], sarcoidosis [74], or chronic uveitis [75]. Some studies have shown an increased incidence of uveitis in patients treated with etanercept for ankylosing spondylitis [76–78]. In general, the efficacy of etanercept for uveitis is poor, and several studies have shown that other TNF inhibitors (adalimumab and infliximab) are more effective and preferred for the treatment of uveitis as discussed below [79, 80].

Administration and dosing: Enbrel (Immunex, Thousand Oaks, CA) is the brand name for etanercept, and it is typically administered subcutaneously at a dose of 50 mg every 1–2 weeks or 0.8 mg/kg weekly. It was first approved by the FDA in 1998 for the treatment of rheumatic diseases.

Adverse effects: Side effects of etanercept can include localized effects such as pain and swelling at the injection site [81]. There are reported cases of an increased risk of fungal infection and TB reactivation [78, 82]. Some reports have shown exacerbation of uveitis or development of uveitis concurrent with etanercept treatment [78, 82]. Other serious side effects include lupus-like disease due to autoantibodies generated against etanercept, exacerbation of the central and peripheral nervous system demyelinating disorders, hematologic, and cardiovascular side effects [81, 83, 84]. Please see full prescribing information for complete list.

Contraindications: Sepsis [85]. Tuberculosis reactivation or newly acquired tuberculosis has been reported to have an increased incidence in patients on TNF inhibitors [86, 87]; additional discussion is provided at the end of this section.

2.2 Adalimumab

Adalimumab was the first fully human IgG1 monoclonal antibody to be approved by the FDA. It was approved as an antibody against TNF-α following the development of infliximab and etanercept. Adalimumab inhibits TNF-α activity by directly binding TNF-α to prevent it from interacting with TNF receptors [88]. Adalimumab is FDA approved for the treatment of RA, inflammatory bowel disease, PA, JIA, and AS [89]. Several prospective and retrospective studies report the efficacy of adalimumab in the treatment of uveitis. In a prospective VISUAL I and VISUAL II study (2010 to 2015) of 217 and 226 adult patients with active and inactive uveitis, respectively, Sheppard et al. found significant improvement in clinical outcomes in patients treated with adalimumab compared to the placebo group [90]. Also, a prospective study from 2006 to 2011 showed that 17 out of 19 adult patients with refractory uveitis in Behcet's disease achieved clinical improvement [91]. Similar results were observed in another prospective study with 72 adult patients conducted between 2006 and 2012 [92]. This study reported that adalimumab reduced the frequency of uveitis attacks in patients with AS by 72% [92]. Another prospective study with 31 refractory uveitis patients reported 68% of these patients showed resolution of ocular inflammation at 10 weeks of treatment and after 1 year 39% of these patients maintained remission [93]. Similarly, in a retrospective study, the efficacy and safety of adalimumab in Behcet's disease-related uveitis were reported using records of 40 patients treated with adalimumab for up to 12 months [94]. The retrospective chart review showed remission was achieved in 95% of the patients [94]. The use of adalimumab in pediatric patients was reported in a prospective study with 18 young patients (2–19 years) with chronic anterior uveitis; 88% of the patients responded to the therapy [95]. Similar results were reported in another pediatric study including 90 children and adolescents; this study shows responsiveness to adalimumab and lower treatment failure compared to a placebo treatment [96].

In 2014, the executive committee of the American Uveitis Society recommended adalimumab as a first-line treatment for uveitis associated with Behcet's disease when uncontrolled by standard immunomodulatory drugs [24]. Importantly, in 2016, adalimumab became the first and the only drug to be FDA approved for the treatment of intermediate, posterior, and panuveitis [97].

Administration and dosing: Adalimumab is sold under the brand name Humira (AbbVie Inc., North Chicago, IL), and Amjevita is a biosimilar (Amgen, Inc., Thousand Oaks, CA), but Amjevita is not available in the USA due to patent issues, and it is typically given subcutaneously every 1–2 weeks at a dose of 40–80 mg or 20 mg if the body weight is less than 30 kg.

Adverse effects: In some of the studies mentioned above, adalimumab treatment for uveitis was associated with some severe side effects. These serious side effects include sarcoidosis, anaphylaxis, optic neuritis, Guillain-Barre syndrome, multiple sclerosis, adenoma, and melanoma [83, 91, 98–100]. Please see full prescribing information for complete list.

Contraindications: None are listed with the FDA [101]. Tuberculosis reactivation or newly acquired tuberculosis has been reported to have an increased incidence in patients on TNF inhibitors [86, 87]; additional discussion is provided at the end of this section.

2.3 Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody that contains the human constant region and murine variable regions, and it binds both membrane-bound and free TNF-α [102]. This drug was initially developed and approved by the FDA

in 1998 for the treatment of inflammatory bowel disease; subsequently, this drug was approved for the treatment of RA and other rheumatoid diseases [103, 104]. Clinical trials to assess the efficacy of infliximab as a treatment for uveitis demonstrate that it is a potential treatment option. One prospective study reported a rapid response to infliximab in six adult patients that had uveitis associated with Behcet's disease or sarcoidosis [105]. Similarly, in another prospective study, 9 out of 11 patients with refractory posterior uveitis showed improvement of disease following treatment with infliximab [106]. Efficacy of infliximab in pediatric patients with uveitis has been demonstrated in retrospective studies of JIA patients [107, 108]. All 17 patients in one study showed a rapid and well-tolerated response to infliximab [108]. Also, several studies have demonstrated the effectiveness of infliximab in localized uveitis as well as systemic autoimmune diseases associated with uveitis. One prospective study demonstrated effective suppression of uveitis in 18 out of 23 patients at 10 weeks of treatment initiation, and clinical success was achieved in all patients at week 50 [109].

Numerous clinical trials have compared the efficacy between adalimumab and infliximab in the treatment of noninfectious uveitis; most of these studies concluded that, overall, both anti-TNF-α agents showed equivalent efficacies. In one study, 160 patients with refractory uveitis were treated with either infliximab or adalimumab, 93% of the patients achieved remission after 12 months of treatment, and no significant difference in terms of occurrence of uveitis was seen between the two treatment groups [110]. Also, the expert panel from the American Uveitis Society recommends infliximab or adalimumab as the first-line treatment for uveitis in Behcet's disease [24].

Administration and dosing: Infliximab is sold under the brand name Remicade (Janssen Biotech, Horsham, PA) and is typically given intravenously at a dose of 3–5 mg/kg at weeks 0, 2, 6, and subsequently every 8 weeks [24].

Adverse effects: The most notable side effect of infliximab in some patients was generation of autoantibody against the non-humanized component of the drug [111]. Other serious side effects include an increased risk of lymphoma, reactivation of TB, and an increased risk of fungal infections [82]. Infliximab may also contribute to the exacerbation of demyelinating diseases and is not preferred in patients with multiple sclerosis [112, 113]. Please see full prescribing information for complete list.

Contraindications: Heart failure has been reported with doses greater than 5 mg/kg. Severe hypersensitivity to Remicade or to inactive components of Remicade or to proteins of mouse origin has been reported [114]. Tuberculosis reactivation or newly acquired tuberculosis has been reported to have an increased incidence in patients on TNF inhibitors [86, 87]; additional discussion is provided at the end of this section.

2.4 Golimumab

Golimumab is a promising TNF-α inhibitor for the treatment of autoimmune uveitis. It is a fully humanized IgG1 monoclonal antibody that binds to both soluble and membrane-bound TNF-α. This antibody has greater TNF-α binding affinity than infliximab and adalimumab [115]. This drug was FDA approved for the treatment of ulcerative colitis, RA, PA, and AS in 2013 [116]. The success of other TNF-α inhibitors (adalimumab and infliximab) in the treatment of uveitis paved way for the use of golimumab in uveitis [117]. Retrospective and prospective studies of golimumab in uveitis showed promising results of its effectiveness in maintaining remission. Retrospective analysis of the efficacy of golimumab in patients with recurrent uveitis between 2013 and 2015 showed remission achieved in 12 eyes

out of 15 after a median follow-up period of 11 months [118]. A prospective study of 15 patients with refractory uveitis related with spondyloarthritis demonstrated the effectiveness of golimumab in uveitis. The results from this study showed rapid improvement of intraocular inflammation in most of the patients with chronic or relapsing uveitis including patients that were refractory to other TNF-α inhibitors [119].

Administration and dosing: Golimumab is marketed under the brand name Simponi (Janssen Biotech, Horsham, PA) and is given subcutaneously at a dose of 50 mg once a month or 200 mg then 100 mg at week 2 and 100 mg every 4 weeks for UC. It can be given intravenously at a dose of 2 mg/kg at week 0 and 4 and then every 8 weeks.

Adverse effects: Golimumab as with other TNF-α inhibitors interferes with the inflammatory response, so the use of this drug is associated with side effects similar to those seen in other TNF-α, specifically increased risk of bacterial infections and reactivation of TB [120–122]. When golimumab is combined with antimetabolites such as azathioprine or 6-mercaptopurine, it can lead to an increased risk of malignancies [123]. Please see full prescribing information for complete list.

Contraindications: None are listed with the FDA [124]. Tuberculosis reactivation or newly acquired tuberculosis has been reported to have an increased incidence in patients on TNF inhibitors [86, 87]; additional discussion is provided at the end of this section.

2.5 Certolizumab

Certolizumab is a member of the TNF-α inhibitors that was developed and approved by the FDA for the treatment of Crohn's disease and RA in 2008 and 2009, respectively [125]. Certolizumab pegol is a humanized antigen-binding fragment (Fab) of monoclonal antibody that targets TNF-α and lacks the Fc region. The Fab fragment is conjugated to polyethylene glycol to increase the half-life of certolizumab compared to other TNF inhibitors [2]. Interest in effectiveness of certolizumab in the treatment of uveitis occurred as an indirect consequence of treatment of systemic diseases associated with uveitis [126]. A retrospective study reported the effectiveness of certolizumab in uveitis, which highlighted the efficacy of certolizumab in five of seven patients with uveitis refractory to other anti-TNF-α agents [126]. Prospective studies are ongoing to test the efficacy of certolizumab in anterior uveitis (NCT03020992 clinicaltrials.gov).

Administration and dosing: Certolizumab is marketed under the trade name Cimzia (UCB, Brussels, Belgium). It is administered subcutaneously at a dose of 400 mg at weeks 0, 2, and 4 and then 200–400 mg every 4 weeks.

Adverse effects: Studies of the effectiveness of certolizumab in the treatment of autoimmune diseases including uveitis have recorded serious side effects that include new-onset uveitis [127, 128]. Others have observed worsening of arthritis symptoms following treatment with certolizumab. Other serious side effects include increase risk of infection, lupus-like syndrome, and cancer [129]. Please see full prescribing information for complete list.

Contraindications: Serious hypersensitivity reaction to certolizumab pegol or the inactive components has been reported [130]. Tuberculosis reactivation or newly acquired tuberculosis has been reported to have an increased incidence in patients on TNF inhibitors [86, 87]; additional discussion is provided at the end of this section.

TNF inhibitors suppress the signals that occur early in the inflammatory cascade and with the exception of etanercept have produced remarkable

outcomes in uveitis. Currently, adalimumab and infliximab have been shown to be effective in the treatment of refractory uveitis especially in Behcet's disease-related uveitis or JIA. However, only adalimumab is approved by the FDA for the treatment of uveitis. Because uveitis has occurred in patients being treated with etanercept for autoimmune disease, it is not recommended for the treatment of uveitis [127]. The reactivation of latent tuberculosis or newly acquired tuberculosis is not listed as a contraindication by the FDA, but there are multiple reports that the incidence of tuberculosis reactivation or newly acquired infection is greater in patients on TNF inhibitor therapy [86, 87]. As such, tuberculosis screening before initiation of TNF inhibitor therapy and routine screening for tuberculosis are highly recommended. Additional clinical outcome data from large population studies will be required to demonstrate the safety and efficacy of golimumab and certolizumab. The effectiveness and utilization of TNF-α inhibitors in the treatment of uveitis are limited by the huge cost of these drugs, limited outcome data on clinical use of TNF-α inhibitors in some disease-specific uveitis, and severe side effects in some cases.

3. IL-1 inhibitors

The biological agents classified as IL-1 inhibitors target and inhibit the proinflammatory cytokine, IL-1β, and its receptor, IL-1R. IL-1 is a strong proinflammatory cytokine that plays a role in both local and systemic immune responses and is also involved in tissue damage during chronic inflammation [131, 132]. IL-1 mediates its inflammatory response through IL-1α and IL-1β. The latter has been reported to be a critical mediator of autoimmunity when compared with IL-1α [133]. IL-1β is secreted by innate immune cells such as macrophages, neutrophils, dendritic cells, and vascular endothelial cells [55]. IL-1β signals through the IL-1 receptor (IL-1R) to produce its inflammatory effects such as differentiation and expansion of antigen-specific T cells, cell maturation, and induction of acute-phase reaction [134]. This cytokine signaling is known to play a role in autoimmune diseases as demonstrated clinically with significantly elevated levels of IL-1β in biological samples including tears of uveitis patients compared to healthy controls [135]. Also, high levels of this cytokine are implicated in some systemic autoimmune diseases including those associated with uveitis [131].

Studies have shown that loss of IL-1 signaling provides protection from uveitis in animal models of autoimmune uveitis [131]. Being a pleiotropic cytokine, IL-1 activity is tightly regulated by a naturally occurring antagonist of IL-1 receptor (IL-1RA) which specifically inhibits the activities of IL-1 cytokines through blockade of IL-1 receptor. Under physiologic conditions, balance exists between the specific receptor antagonist and IL-1. However, imbalance in the levels of IL-1 and/or IL-1 RA can increase the risk of developing immune-mediated diseases [136]. Also, exogenous administration of IL-1RA in animal models showed inhibition of IL-1 signaling events [136]. Biological agents such as recombinant IL-1R antagonist (anakinra) which mimics the activity of IL-RA have been developed and have shown great success in the reduction of autoimmune diseases [137, 138]. Other biological agents such as soluble decoy IL-1 receptor (rilonacept) and neutralizing monoclonal antibodies (canakinumab and gevokizumab) that have specific inhibition of IL-1 activity have also been utilized in the treatment of autoimmune diseases. Suppression of ocular inflammation may be achieved due to the efficacy of IL-1β inhibitors in the control of inflammation in systemic autoimmune diseases that are associated with uveitis. Additional discussion of these inhibitors is provided below.

3.1 Anakinra

Anakinra was first introduced in 1993 (Kineret, Amgen Inc., Thousand Oaks, California), and it is a recombinant non-glycosylated human IL-1RA. It was first approved for the treatment of RA and neonatal-onset multisystem inflammatory disease (NOMID) by the FDA in 2001 [139]. There is limited data on the use of anakinra in the treatment of uveitis; however, a few case studies have reported its effectiveness in uveitis. One study looked at its effect as a treatment for NOMID, which is associated with childhood uveitis; anakinra produced resolution of ocular symptoms in addition to the systemic disease improvement. In this case study, a 4-year-old with chronic infantile neurological cutaneous articular (CINCA) syndrome that is associated with uveitis, who had a poor response to TNF-α inhibitors, showed a significant sustained improvement with anakinra [140]. Another case series also demonstrated the effectiveness of anakinra in two patients with anterior uveitis due to exposure to etanercept or uveitis refractory to infliximab [141]. Also, a retrospective study of 19 patients with Behcet's disease-related uveitis showed effective control of inflammation and improvement in ocular symptoms after 12 months of treatment with anakinra [142].

Administration and dosing: Anakinra is sold under the brand name Kineret (Swedish Orphan Biovitrum Stockholm, Sweden) and is given subcutaneously at a dose of 100 mg daily or up to 8 mg/kg a day.

Adverse effects: Anakinra is associated with side effect that ranges from a local reaction at the injection site to more severe side effects such as hepatitis, neutropenia, and increase risk of infection [143–145]. Another side effect that could occur is the generation of autoantibodies against anakinra [146]. Please see full prescribing information for complete list.

Contraindications: Serious hypersensitivity reaction to *E. coli*-derived proteins, Kineret, or the inactive components [147].

3.2 Canakinumab

Canakinumab is a human monoclonal antibody against IL-1β that was first approved by the FDA in 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS), and, subsequently, it was approved for the treatment of SJIA and JIA in 2013 [148, 149]. Canakinumab inhibits IL-1β by directly binding and neutralizing IL-1β signaling. The long-term effectiveness of canakinumab as a treatment for uveitis has not been studied. However, several case studies show canakinumab as a potential therapeutic for refractory uveitis. Successful resolution of inflammation with canakinumab treatment was seen in a case report of a 64-year-old patient with CAPS-associated uveitis [150]. Another case series by Brambilla et al. (2016) showed successful treatment of refractory uveitis with canakinumab in two children. The first patient in this study was a 9-year-old with recurrent uveitis associated with JIA intolerant to TNF-α inhibitors and refractory to other immune modulatory drugs. Clinical improvement was achieved within 12 months of initiating canakinumab [25]. The second patient, a 6-year-old boy with bilateral uveitis refractory to TNF-α inhibitors, showed a faster responsiveness with remarkable improvement to canakinumab within 2 months of treatment [25]. Another case study of a 16-year-old with severe Behcet's disease associated refractory panuveitis, responded to a single dose of canakinumab with remission of uveitis for at least 8 weeks [151]. Overall, the case series provides evidence of the effectiveness of canakinumab for the treatment of uveitis. In addition, a retrospective study of 19 patients with BD-related uveitis showed an improvement of ocular symptoms after 12 months of treatment with canakinumab [142].

Additional prospective and retrospective studies in large patient groups are needed to validate the effects of canakinumab in uveitis.

Administration and dosing: Canakinumab is marketed as Ilaris (Novartis, East Hanover, NJ) and given at a dose of 150–300 mg subcutaneously every 4 weeks or 2–4 mg/kg every 4 weeks.

Adverse effects: Side effects of this drug include an increased risk of infection [152, 153]. Please see full prescribing information for complete list.

Contraindications: Serious hypersensitivity to Ilaris or the inactive components [154].

3.3 Gevokizumab

Gevokizumab is a humanized recombinant IgG2 monoclonal antibody with high affinity for IL-1β. Its ability to bind strongly to IL-1β prompted interest in its use as a biological agent for autoimmune uveitis. A prospective study of eight patients with anterior scleritis showed improvement in symptoms in seven of the patients following treatment with 60 mg SC of gevokizumab every 4 weeks for 12 weeks and continued to show improvement for 36 more weeks [155].

Gul et al. conducted a prospective study to test the efficacy of gevokizumab in patients with acute exacerbation of resistant uveitis in Behcet's disease. Seven adult patients were given a single intravenous gevokizumab infusion at a dose of 0.3 mg/kg. All patients experienced a rapid clinical response and resolution of intraocular inflammation within a median duration of 14 days [156]. Gul et al. also conducted another prospective study to test the efficacy and safety of gevokizumab in 21 patients with Behcet's disease-related uveitis; 3 patients were withdrawn from the study due to exacerbation of uveitis, but 14 patients showed responsiveness within 21 days [157]. These studies provide evidence of the effectiveness of gevokizumab in uveitis, especially the Behcet's-related uveitis. However, the EYEGUARD clinical trials did not show efficacy of gevokizumab in the treatment of uveitis [158]. In the EYEGUARD study, 83 patients with Behcet's disease-related uveitis were recruited into the study. Study groups were given 60 mg of gevokizumab every 4 weeks subcutaneously and were well tolerated. However, the results from this study did not show any treatment efficacy of gevokizumab compared to the placebo group [158]. The conflicting results from these two studies may be due to the route of administration with intravenous infusion being superior to subcutaneous administration. As such, further studies on the dosage, long-term efficacy, and safety of gevokizumab for uveitis treatment are necessary.

Administration and dosing: XOMA 052 (XOMA Corporation, Berkeley, CA, USA) is the brand name of gevokizumab. It has not been FDA approved but in trials has been administered at a dose of 60 mg IV or SC every 4 weeks.

Adverse effects: Gevokizumab is generally tolerated; however, it can result in mild side effects that include injection site reaction, neutropenia, and hypoglycemia [155, 159]. Please see full prescribing information for complete list.

Contraindications: None are listed with the FDA because it is not yet FDA approved.

3.4 Rilonacept

Rilonacept is a fully humanized IL-1 fusion protein, and it consists of the ligand-binding domain of the extracellular component of the IL-1 receptor and IL-1 receptor accessory protein. Rilonacept binds to IL-1β to prevent it from interacting with IL-1 receptor, thus preventing IL-1 signaling. This drug is FDA approved for the treatment of autoinflammatory diseases such as familial cold autoinflammatory

syndrome (FCAS) and Muckle-Wells syndrome (MWS) [160]. However, there are no clinical data on the use of rilonacept in uveitis, but it is currently being evaluated as a treatment for uveitis [161].

Administration and dosing: Rilonacept is marketed as Arcalyst by Regeneron Pharmaceuticals, Tarrytown, New York. It is given subcutaneously at a dose of two 160 mg injections at week 0 and then 160 mg/week.

Adverse effects: Local and/or hypersensitivity reaction [162, 163]. Other side effects reported include gastrointestinal bleeding and an increased risk for *Streptococcus pneumoniae* meningitis [160]. Please see full prescribing information for complete list.

Some autoimmune diseases such as rheumatic diseases respond to IL-1β inhibitors. However, the effects of these biologics in uveitis are not conclusive. Some IL-1β inhibitors such as anakinra have demonstrated efficacy in Behcet's disease-related uveitis and autoinflammatory diseases such as NOMID that could be associated with uveitis [139]. Additional large clinical studies are required to evaluate the efficacy of IL-1β as a therapy for autoimmune uveitis.

Contraindications: None listed with the FDA [164].

4. IL-6 inhibitors

IL-6 is a powerful proinflammatory cytokine that is secreted by both innate and adaptive immune cells (B and T cells). Due to its pleiotropic effects including T-cell activation, IL-6 is implicated in many T-cell-mediated diseases [7]. Biological agents that inhibit IL-6 have been used as a treatment for autoimmune diseases such as RA and JIA. In spite of the proinflammatory effects, it has a role in tumor survival, so blockage of IL-6 is also effective as a cancer treatment, particularly large-cell lung cancer and ovarian cancer [165].

4.1 Tocilizumab

Tocilizumab is a fully humanized monoclonal antibody against both soluble and membrane-bound IL-6 receptors. It is currently FDA approved for the treatment of SJIA and RA, and it has profoundly improved disease outcomes [166]. A study by Tappeiner et al. has reported that two out of three patients with JIA-related uveitis responded to tocilizumab that was refractory to anti-TNF-α therapy [167]. Furthermore, a retrospective study that analyzed disease outcomes in five patients with refractory uveitis showed sustained remission after a mean follow-up period of 8.4 months [168]. A similar outcome was observed in another study testing the efficacy of tocilizumab to treat refractory uveitis with 10 out of 17 patients responding to IL-6 blockade [169]. A prospective STOP-UVEITIS study to test the safety, tolerability, and efficacy of tocilizumab in 37 patients with noninfectious uveitis was conducted by Quan et al. (2017); the result of this study shows tolerance at 6 months of drug initiation [170]. These studies and several case studies have reported that tocilizumab may be effective in the treatment of refractory uveitis [171, 172]. Also, Ruiz-Medrano et al. compiled data on the use of tocilizumab in the treatment of ocular conditions between 2011 and 2017. They found that tocilizumab is effective in the treatment of variety of ocular inflammatory conditions including refractory uveitis [173].

Administration and dosing: Tocilizumab (Actemra, Genentech, South San Francisco, CA, USA) is typically administered at a dose of 4–12 mg/kg every 2–4 weeks when given intravenously and 162 every 1–2 weeks when given subcutaneously.

Adverse effects: Side effects from Actemra include neutropenia with increased risk of fungal and bacterial infections and opportunistic infections [174]. Other side effects include hypersensitivity, increased risk of gastric perforation, and malignancies [175–177]. Please see full prescribing information for complete list.

Contraindications: Hypersensitivity to Actemra [178]. Tuberculosis reactivation has been reported in patients undergoing IL-6 inhibitor therapy [179], so patients should be initially tested for latent tuberculosis and should be routinely monitored for newly acquired tuberculosis.

Biological Target/ Pathway	Generic name	Brand name	Specific Target	Company	Route	Manufacturer Suggested Dose	Indications (FDA approved)	FDA approved for uveitis
TNF-α	Etanercept	Enbrel	soluble TNF-α and β	Amgen, Thousand Oaks, CA	SC	50 mg every 1-2 week(s) or 0.8 mg/kg weekly	RA, PA, PP, JIA, AS	Not recommended for Uveitis
	Adalimumab	Humira	TNF-α	Abbvie Inc., North Chicago, IL.	SC	40-80 mg every 1- 2 week(s)	RA, JIA, PA, AS, Crohn's, UC, PP, HS, uveitis	Approved for uveitis, 2016
	Infliximab	Remicade	TNF-α	Janssen Biotech Inc., PA	IV	3-5 mg/kg every 2 weeks for 6 weeks then once every 8 weeks	Crohn's, UC, RA, AS, PA, PP	Not FDA approved for Uveitis
	Golimumab	Simponi	TNF-α	Janssen Biotech Inc., PA	SC or IV	SC: 50 mg once a month; 200 mg then 100 mg at week 2, and 100 mg every four weeks for UC IV: 2 mg/kg at week 0 and 4, then every 8 weeks	UC (not for IV), RA, PA, AS	Not FDA approved for Uveitis
	Certolizumab pegol	Cimzia	TNF-α	UCB Pharma Inc., Brussels, Belgium	SC	400 mg every 2 weeks for 4 weeks then 200-400 mg every 2-4 weeks	Crohn's disease, RA, PA, AS, PP	Not FDA approved for Uveitis
IL-1β	Anakinra	Kineret	IL-1β	Swedish Orphan Biovitrum, Sweden	SC	100 mg daily or up to 8 mg/kg daily	RA, NOMID, CAPS	Not FDA approved for uveitis
	Canakinumab	ILaris	IL-1β	Novartis, Basel, Switzerland	SC	150-300 mg once a month or 2-4 mg/kg every 4 weeks	CAPS, TRAPS, HIDS/MKD, FMF	Not FDA approved for Uveitis
	Gevokizumab	XOMA 052	IL-1β	Novartis, Basel, Switzerland	SC or IV	60 mg /month	In development	Not FDA approved for Uveitis
	Rilonacept	Arcalyst	IL-1β	Regeneron, Tarrytown, New York	SC	160 mg/week with 320 mg loading dose at week 0	CAPS, FCAS, MWS	Not FDA approved for uveitis
IL-6	Tocilizumab	Actemra	IL-6 receptor	Genetech Inc., CA	IV or SC	IV: 4-12 mg/kg every 2-4 weeks SC: 162 mg every 1-2 week(s)	GCA, SJIA, RA, PJIA, cytokine release syndrome	Not FDA approved for uveitis
	Sarilumab	Kevzara	IL-6 receptor	Regeneron/Sanofi NY	SC	200 mg every 2 weeks	RA	Not FDA approved for uveitis
	Olokizumab	Not yet assigned	IL-6	UCB Pharma Inc., Belgium / Licensed to R-Pharma, Moscow, Russia	SC	64 mg every 2 or 4 weeks	RA - Clinical trial NCT02760368 to be completed January 2019	Not FDA approved for uveitis
	Clazakizumab	Not yet assigned	IL-6	Vitaeris, Vancouver, Canada	SC	5- 25 mg	In development	Not FDA approved for uveitis
	Siltuximab	Sylvant	IL-6	Janssen Biotech, PA	IV	11 mg/kg every 3 weeks	Castleman's disease	Not FDA approved for uveitis
IL-17	Secukinumab	Cosentyx	IL-17A	Novartis, Basel, Switzerland	SC	150-300 mg weekly for 4 weeks, then once a month	PP, AS, PA	Not FDA approved for uveitis
	Ixekizumab	Taltz	IL-17A	Eli Lilly and Co, Indianapolis, IN	SC	160 mg every 2 weeks for 3 months then 80 mg once a month or 160 mg at week 0 then 80 mg every 4 weeks	PP, PA	Not FDA approved for uveitis
	Brodalumab	Siliq	IL-17 receptor	Bausch Health, Laval, Canada	SC	210 mg weekly for 3 weeks then once every 2 weeks	PP	Not FDA approved for uveitis

Table 1.
List of biologics discussed in sections 3–6.

4.2 Sarilumab

Sarilumab is another IL-6 receptor inhibitor, it is a fully humanized monoclonal antibody against the alpha subunit of the IL-6 receptor, and in 2017 it was FDA approved as a treatment for RA [180]. Sarilumab has shown some potential as an effective therapy for autoimmune uveitis in a prospective SATURN study [181]. In this randomized study, 57 patients with posterior uveitis on steroids with or without methotrexate were treated with 200 mg of sarilumab or placebo every 2 weeks. About 64% of the patients on sarilumab showed clinical improvement and steroid-sparing effects at 16 weeks after treatment initiation [181].

Administration and dosing: Sarilumab is marketed as Kevzara (Regeneron/Sanofi Tarrytown, NY, USA), and in the treatment of RA, sarilumab is typically given at 200 mg SC every 2 weeks.

Adverse effects: Increased risk of GI perforation and hepatitis [182]. Please see full prescribing information for complete list.

Contraindications: Hypersensitivity to Kevzara or the inactive ingredients [183]. Tuberculosis reactivation has been reported in patients undergoing IL-6 inhibitor therapy [179], so patients should be initially tested for latent tuberculosis and should be routinely monitored for newly acquired tuberculosis.

Other IL-6 inhibitors: Olokizumab (UCB, Brussels, Belgium) and clazakizumab (Alder Biopharma, Bothell, WA, USA) are currently being evaluated in clinical trials for the treatment of autoimmune diseases (which can be associated with uveitis) such as RA. Siltuximab (Janssen, Horsham, PA, USA) has been FDA approved for the treatment of Castleman's disease [184–187]. However, there are little or no data regarding the efficacy of these drugs in uveitis. See **Table 1** for additional information regarding these drugs.

5. IL-17 inhibitors

IL-17 is a proinflammatory cytokine produced by Th17 cells, a subset of inflammatory T cells, involved in an inflammatory response to self and certain extracellular bacteria and fungi. While IL-17 can be produced by other cells, it is the characteristic cytokine produced by Th17 cells. IL-17 is involved in the recruitment and activation of neutrophils [188, 189]. Animal and human studies have elucidated the critical role of IL-17 in the pathogenesis of autoimmune diseases including uveitis [190, 191]. Inhibitors of IL-17 have produced remarkable improvement in the outcome of autoimmune diseases especially rheumatoid diseases [192]. IL-17 inhibitors such as secukinumab (AIN457), ixekizumab (Taltz), and brodalumab (AMG 827) are FDA approved for the treatment of severe psoriasis [193]. Knowledge of the efficacies of these biological agents in autoimmune diseases provides the potential for use in uveitis, especially uveitis that is refractory to conventional drugs and other biologics. Blockade of IL-17 in animal models of autoimmune uveitis has produced significant improvement in uveitis symptoms [194].

5.1 Secukinumab

Secukinumab is a fully humanized monoclonal antibody that neutralizes IL-17A. It is FDA approved for treatment of moderate to severe plaque psoriasis [195]. Hueber et al. tested the efficacy of AIN457 in a prospective study with 104 uveitis patients, RA or psoriasis. About 50% of the uveitis patients showed a rapid response within 2 weeks and by 8 weeks of drug initiation; 13 out of 16 patients responded to AIN457 [196]. In a prospective study of 118 patients with Behcet's disease (SHIELD

study), the rate of recurrent ocular exacerbation of uveitis did not differ between the patients that received secukinumab or placebo. The study concluded that secukinumab did not demonstrate efficacy in the treatment of uveitis. Similar outcomes were concluded from the INSURE and ENDURE studies in which altering the dosing schedule of secukinumab did not improve the efficacy of secukinumab in uveitis patients [197, 198]. The outcome of these studies may have differed from the initial report by Hueber et al. because the differences were noted in the patient disease profile, concomitant immunosuppressive therapies, and route of administration [197]. One prospective study demonstrated that intravenous secukinumab (10 mg/kg or 30 mg/kg) had better efficacy than subcutaneous secukinumab (300 mg). Therefore, these studies demonstrate that patients responded better to secukinumab when it was administered IV [198].

Administration and dosing: Secukinumab was initially named AIN 457 and has been renamed Cosentyx (Novartis). It is given subcutaneously for plaque psoriasis at a dose of 150–300 mg weekly for 4 weeks and then every 4 weeks. However, it has been suggested that it is more effective given IV at 30 mg/kg for the treatment of noninfectious uveitis [198].

Adverse effects: Cosentyx is associated with an increased risk of infection, hypersensitivity reaction, and inflammatory bowel disease [199, 200]. Please see full prescribing information for complete list.

Contraindications: Hypersensitivity to Cosentyx or any of the inactive ingredients [201]. Tuberculosis reactivation is listed as a warning by the FDA, but it has been reported in a multicenter retrospective study by Novartis [202] and in a review of the literature [203] that there is no increased risk of tuberculosis reactivation.

Other IL-17 inhibitors: Additional biologics that target the IL-17 pathway include ixekizumab and brodalumab. Ixekizumab targets IL-17A and is FDA approved to treat plaque psoriasis and psoriatic arthritis. Brodalumab targets the IL-17 receptor and is FDA approved for the treatment of plaque psoriasis. At the time of this review, clinical trials for uveitis are underway, so there are no clinical reports regarding their efficacy in autoimmune uveitis. See **Table 1** for additional information regarding these drugs.

6. Other biologics

Biological agents that target and inhibit cytokines such as TNF-α and IL-1β have been extensively studied and have resulted in improving clinical outcomes in many autoimmune diseases including uveitis. We chose to include a more in-depth discussion of biologics that target IL-6 and IL-17 because IL-6 is such a central inflammatory cytokine that bridges both innate and adaptive immunities, and IL-17 is the characteristic cytokine produced by Th17 T cells that are involved in autoimmune diseases. The efficacies of these biological agents have spurred the introduction of additional biologics that target other inflammatory mediators implicated in autoimmunity. Also, the heterogeneity of uveitis, non-responsiveness or adverse effects associated with the current biologics used for the treatment of uveitis, provides the need to examine the efficacy of other biological agents that target other mediators implicated in autoimmunity. Recombinant interferon and IVIG are biologics used for the treatment of refractory autoimmune uveitis and other inflammatory conditions [204–206]. However, the precise mechanism of action for these medications is not well understood. Rituximab targets CD20 on B cells and is used for the treatment of ocular cicatricial pemphigoid, scleritis, and uveitis associated with granulomatosis with polyangiitis [207, 208]. There are also additional biologics

that target specific cytokines and cell surface proteins that are in development and undergoing clinical trials for autoimmune diseases that may include uveitis, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, and others. Since these other biologics are still in various phases of development, we will not go into the same level of detail as in the others discussed above. Because there are many medications that are not public knowledge, the following is not an exhaustive list. Some of the medications that may be available for the treatment of autoimmune uveitis in the near future target IL-15, IL-23 p40, interferon, and its receptors, CD52, CD4, VEGF, and VCAM. A fusion protein consisting of the B7-binding portion of CTLA4 and IgG is also available and is being evaluated for the treatment of autoimmune uveitis.

7. Switching biological therapies

The development of multiple biologics that target specific inflammatory pathways has greatly increased the treatment options available for patients with autoimmune uveitis. With so many options available, it is of interest to determine if there is an advantage to switching the biologic, either within the same class or to a different class. Large clinical studies have not been done with uveitis cohorts, but some have been done with rheumatoid arthritis patients. There is some evidence that switching biologics within the same class, specifically related to TNF-α inhibitors, for reasons related to adverse reactions rather than efficacy may be beneficial [209]. A more recent study found that switching from TNF-α inhibitors to another biological class showed a significantly greater benefit than switching to another TNF-α inhibitor [210]. Therefore, it is still not clear which is the best biological treatment strategy for autoimmune uveitis patients, but there is some indication based on RA patients that switching to a different class of biologics may have significantly better outcomes than switching to another biological within the same class.

8. Conclusions

In this review, we focus on biologics that target TNF-α, IL-β, IL-6, and IL-17. The rationale for this is that TNF-α, IL-β, and IL-6 cytokines are involved in key inflammatory pathways that target both the innate and adaptive arms of the immune response. We also include a brief discussion of IL-17 because it is produced by a specific T-cell subset, and Th17 cells have been demonstrated to be involved in autoimmune diseases [190, 191]. There are other biologics that target other cytokines and cell types, but these are in earlier phases of development and are not yet FDA approved. Additional options for therapy are constantly being studied. Biologics are a newer class of therapeutics that have the advantage over other medications in that they are extremely specific for one target molecule. This specificity makes them attractive as therapeutics because specific pathways and/or cell types can be blocked. Inhibition of a specific pathway or cell type has the advantage over other immunosuppressive therapies that suppress all leukocytes and lymphocytes. A drawback to biologics is the high economic burden associated with these drugs. Because of the high cost associated with biologics, it can be difficult to obtain insurance coverage until multiple therapies have failed. As such, the cost to the patient could be a permanent loss of vision with repeated relapses and the use of corticosteroids while transitioning to a new therapy. Importantly, because these therapies have efficacy in treatment of systemic autoimmune diseases such as RA,

inflammatory bowel diseases, and Behcet's disease with a uveitis manifestation they may be effective for the majority of uveitis patients that only have ocular involvement [2, 211]. Therefore, additional appropriately powered clinical studies are necessary to demonstrate the effectiveness of biologics for the treatment of chronic autoimmune uveitis.

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List of abbreviations

APCs	antigen-presenting cells
AS	ankylosing spondylitis
AU	autoimmune uveitis
BD	Behcet's disease
CAPS	cryopyrin-associated periodic syndromes
CINCA	chronic infantile neurological cutaneous articular
CLL	chronic lymphocytic leukemia
FCAS	familial cold autoinflammatory syndrome
FDA	Food and Drug Administration
FMF	familial Mediterranean fever
GCA	giant cell arteritis
HIDS	hyperimmunoglobulin D syndrome
HLA	human leukocyte antigen
HS	hidradenitis suppurativa
IgG	immunoglobulin G
IL-17	interleukin-17
IL-1b	interleukin-1 beta
IL-6	interleukin-6
JIA	juvenile idiopathic arthritis
MKD	mevalonate kinase deficiency
MS	multiple sclerosis
mTOR	mammalian target of rapamycin
MWS	Muckle-Wells syndrome
NHL	non-Hodgkin lymphoma
NOMID	neonatal-onset multisystem inflammatory disease
NSAIDs	nonsteroidal anti-inflammatory drugs
PA	psoriatic arthritis
PJIA	polyarticular juvenile idiopathic arthritis
PP	plaque psoriasis
RA	rheumatoid arthritis
SJIA	systemic juvenile idiopathic arthritis

TLR	toll-like receptor
TNF-a	tumor necrosis factor-alpha
TRAPS	tumor necrosis factor receptor-associated periodic syndrome
UC	ulcerative colitis

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