**Review Article**

**Systemic Treatments for Noninfectious Vitreous Inflammation**

**Angela Jiang, 1 Jillian Wang, 1 Malav Joshi, 2 and John Byron Christoforidis 2**

1 Department of Ophthalmology, The Ohio State University Wexner Medical Center, 915 Olentangy River Road, Suite 5000, Columbus, OH 43212, USA  
2 Department of Ophthalmology, The University of Arizona Medical Center, 655 North Alvernon Way, Suite 108, Tucson, AZ 85711, USA

Correspondence should be addressed to John Byron Christoforidis; jbchristo@hotmail.com

Received 18 August 2013; Accepted 26 September 2013

Academic Editor: Mario R. Romano

Copyright © 2013 Angela Jiang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Vitreous inflammation, or vitritis, may result from many causes, including both infectious and noninfectious, including rheumatologic and autoimmune processes. Vitritis is frequently vision threatening, but, today, there are multiple methods of systemic treatment for vitritis. These categories include corticosteroids, antimetabolites, alkylating agents, T-cell inhibitors/calcineurin inhibitors, and biologic agents. These treatment categories were reviewed last year, but, even over the course of just a year, many therapies have made progress, as we have learned more about their indications and efficacy. We discuss here discoveries made over the past year on both existing and new drugs, as well as reviewing mechanisms of action, clinical dosages, specific conditions that are treated, adverse effects, and usual course of treatment for each class of therapy.

1. Introduction

Vitreous inflammation, or vitritis, may result from many causes, including both infectious and noninfectious. Epidemiologic studies indicate that uveitis accounts for 2–10% of prevalent blindness in the European and North American population and is therefore an underrated and significant public health problem [1]. Infectious etiologies include bacterial Lyme, syphilis, or *Bartonella*; viruses HSV, VZV, and CMV, and a variety of fungal and parasitic causes. Noninfectious etiologies include rheumatologic and autoimmune processes, examples being sarcoidosis, systemic lupus erythematosus, multiple sclerosis, and Behcet’s disease. However, idiopathic vitritis without associated systemic disease is most common. Vitritis is sometimes vision-threatening, due to sequelae such as cystoid macular edema (CME), vitreous opacities, and retinal detachment, ischemia/neovascularization, or pigment epithelium changes. Glaucoma and cataracts may also form. With such serious sequelae, there are multiple methods of systemic treatment for vitritis. On the other hand, mild vitritis without vasculitis or CME can sometimes be followed closely without any treatment. The goal of all types of treatment is to rapidly alter and stop the course of intraocular inflammation but at the same time minimize any side effects from these systemic drugs. We reviewed these treatment categories last year, but, even over the course of just a year, many therapies have made progress, as we have learned more about their indications and efficacy [2].

2. Initial Treatment: Corticosteroids

The first line of treatment for noninfectious uveitis is corticosteroids. This group of drugs is used to suppress inflammation, either systemically or intraocular. The accepted algorithm for treatment begins with topical glucocorticoids, with frequency depending upon severity and not necessarily etiology. However, topical corticosteroids have been shown to have poor penetration into the posterior segment and are thus not used often for posterior segment disease; they are more commonly used to reduce anterior chamber inflammation and have only a minor effect on vitreous inflammation [3]. Oral or intravitreal corticosteroids are therefore used to treat cases of posterior segment disease. Oral prednisone (1 mg/kg/day with gradual tapering) is often the first therapeutic agent used [4].
Intravitreal delivery systems include injection or implantation of periocular or intravitreal steroid compounds (triamcinolone acetonide) [5]. There are several different types of systems, either nonbiodegradable or biodegradable; a more extensive review of drug delivery implants is reviewed in our other paper. Although previous studies raised concern for recurrence of inflammation as intravitreal steroid concentration decreases, some recent trials elude that this may no longer be the case [6]. Patients undergoing treatment with local delivery methods will usually have minimal adverse events. It has however been reported that localized side effects may occur, such as cataract formation, increased intraocular pressure, and transient vitreous hemorrhage.

On the other hand, those undergoing systemic corticosteroid therapy often encounter nonocular adverse events, such as arthralgia and hypertension. Other common complications range from those affecting the musculoskeletal system (osteoarthritis, aseptic bone necrosis, and myopathy), gastrointestinal system (ulcers and pancreatitis), endocrine system (hyperthyroidism and cushinoid features), infectious, (delayed wound healing, secondary infection, and reactivation of latent herpes simplex or tuberculosis), or even psychosis. If patients develop adverse effects, or are refractory to treatment with corticosteroid therapy, switching to an intravitreal delivery system or considering systemic immunsuppressive therapy is indicated [7].

### 3. Immunosuppressive Treatment

Systemic immunosuppressive therapy can either supplement or completely replace corticosteroid therapy, for the reasons touched upon above. There are several conditions that have been found to be refractory to corticosteroid treatment but instead respond to immunsuppressives. Examples of these conditions have the gamut of several autoimmune diseases such as Behçet’s, Wegener’s, or juvenile idiopathic arthritis-associated uveitis [8]. Other conditions that indicate immunsuppressive therapy are found in Table 1.

There are several categories of immunosuppressive agents: antimitabolites, alkylating agents, T-cell inhibitors/ calcineurin inhibitors, and biologic agents. Information about these categories is available in Table 2, while newer biologics and investigations are discussed below. Table 3 addresses ocular diseases and which groups of immunosuppressive agents are used to treat them.

In general, treatment with immunsuppressives starts after or with corticosteroid therapy, with local treatment attempted before systemic treatment, if the disease process is amenable. Systemic treatment attempts to start with the least toxic medications in the case of mild-moderate disease; methotrexate and cyclosporine are most commonly used after corticosteroids, followed by more antimitobalites. Severe, vision-threatening disease may require the use of biologic or cytotoxic agents, although they are avoided whenever possible due to their severe adverse effects.

#### 3.1. Leflunomide

Leflunomide is a noncytotoxic drug that works on both the cellular and humoral immune response. It is most commonly used for systemic rheumatologic diseases, examples being severe rheumatoid or psoriatic arthritis. Ocular use in treating chronic inflammation associated with sarcoidosis is currently under investigation [9]. Recently, Leflunomide was proven as both safe and efficacious for long-term therapy treating chronic anterior uveitis associated with juvenile idiopathic arthritis [10]. Most patients maintained an ocular response to the drug and underwent only a few mild adverse effects. Common adverse effects of Leflunomide include hepatotoxicity with known fatalities, myelosuppression with resulting opportunistic infection and anemia, interstitial lung disease, alopecia, and skin reactions (Stevens-Johnson and toxic epidermal necrolysis). Leflunomide is also a teratogen (pregnancy class X), and patients need to be on contraception during treatment. Overall, it is a promising form of treatment, as methotrexate is currently the first and was previously the only choice for patients with juvenile idiopathic arthritis.

#### 3.2. Biologic Agents

Biologic agents are one of the newest classes of therapeutic proteins. They were originally developed for preventing organ transplant rejection but were found to be useful for treating systemic inflammatory diseases as well. They are now used off label in treating uveitis, and have been used with some success for refractory cases. Biologic agents’ major mechanisms of action all revolve around targeting specific inflammatory molecules, with the goal of inhibiting mediators or cytokines. Examples of these inflammatory mediators include tumor necrosis factor alpha and interleukin-2. Due to their strong immunologic suppression, serious adverse effects revolve around infectious processes or malignancies such as lymphoma. Latent and opportunistic infections are especially important to monitor for and include those such as tuberculosis, histoplasmosis, coccidiomycosis and herpes viruses.

Biologic agents are categorized into two groups: monoclonal antibodies and fusion proteins. Monoclonal antibodies are further classified and suffixes named based on their regions (either human, murine, or a combination of regions). Fusion proteins are created by joined genes, and are a combination of a receptor and another protein fragment.

#### 3.2.1. Adalimumab

Adalimumab is a recombinant, full-length humanized immunoglobulin directed against tumor
Table 2: Immunosuppressive agents, organized into categories, and with information on mechanism of action, administration, side effects, and clinical management.

| Mechanism of action | Indications | Administration | Side effects | Management |
|---------------------|-------------|----------------|--------------|------------|
| **Antimetabolites** |             |                |              |            |
| (1) Methotrexate    |             |                |              |            |
| Folic acid analog; dihydrofolate reductase inhibitor, thus inhibiting synthesis of purines and therefore DNA, RNA, thymidylate, and proteins [7]. Reduces T-cell role in inflammation by inhibiting its activation and suppressing intercellular adhesion molecule expression [37]. With all administrations of methotrexate, it is critical to supplement folic acid, to restore thymidylate and purine biosynthesis. | (i) Vitritis (ii) Vasculitides (iii) Anterior uveitis (iv) Orbital pseudo-tumor (v) Sarcoidosis | (i) Oral (ii) Subcutaneous (iii) IM (iv) IV Dose: 75–25 mg/week and May require 3–8 weeks for effects to take full effect. Course: two years after reduction of inflammation, to avoid recurrence [38]. | (i) Common: fatigue, nausea, vomiting, and anorexia [39] (ii) Rare hepatotoxicity, marrow suppression, and vasculitis (cutaneous) (iii) Teratogen Overall, long-term side effect profile is preferable compared to high-dose steroids. | Baseline: CBC, serum chemistry, BUN, Cr, LFT it, UA, pregnancy test. Follow-Up: CBC and LFT’s every 4 weeks, with dose adjustment if LFT’s double on two measurements. Stopped if LFT’s stay elevated even after dose reduction [40]. |
| (2) Azathioprine    |             |                |              |            |
| Imidazolyl derivative; active metabolite is a purine synthesis inhibitor. Since lymphocytes have no method of nucleotide salvage, they are particularly affected [41]. | (i) Serpiginous choroiditis (ii) Multifocal choroiditis (iii) Panuveitis (iv) Ocular cicatricial pemphigoid (v) Juvenile idiopathic arthritis [42–44] | Oral Dose: initially 2-3 mg/kg/day. Course: two years after reduction of inflammation, to avoid recurrence [45]. | (i) GI upset (ii) Hepatotoxicity, bone marrow suppression, alopecia, and pancreatitis [46]. | Baseline: CBC, LFT’s, thiopurine methyltransferase enzyme activity (If low enzyme activity withhold treatment [46].) Follow-Up: CBC and LFT’s every 4–6 weeks, with dose adjustment or temporary stop if abnormalities arise [47]. |
| (3) Mycophenolate mofetil | Reversibly inhibits guanosine nucleotide synthesis, which particularly affects B- and T-cells [48]. it disrupts cellular adhesion to vascular endothelial cells, thus affecting lymphocytic chemotaxis [49]. | (i) Chronic ocular inflammation [50] (ii) Scleritis, uveitis; used with cyclosporine and methotrexate [50]. | (i) GI upset (nausea, vomiting, and diarrhea) (ii) Bone marrow suppression, hepatotoxicity [8] | Baseline: CBC, LFTs Follow-Up: CBC weekly for first month, twice monthly for next two months, and then monthly. LFT’s monthly for duration of treatment [51]. |
| (4) Leflunomide     | Pyrimidine synthesis inhibitor, by inhibiting dihydroorotase dehydrogenase. In this manner, it suppresses B- and T-cell proliferation by interfering with cell cycle progression [52]. Nonlymphoid cells use a salvage pyrimidine pathway to synthesize ribonucleotides [52]. Leflunomide also has proven anti-inflammatory action, due to suppression of lymphocyte proliferation, tyrosine kinase, cyclooxygenase, and histamine release [53, 54]. | Systemic rheumatology (severe rheumatoid and psoriatic arthritis). Ocular use in treating chronic inflammation associated with sarcoidosis is currently under investigation (see main text). | Oral Dose: loading dose100 mg and then 10–20 mg daily. A loading dose may result in initially increased adverse effects, but more rapid efficacy [55, 56]. To increase tolerability, patients may be given prednisolone rather than a loading dose [55]. Course: currently not certain. | (i) Serious hepatotoxicity (jaundice, hepatitis, and fatalities) (ii) Bone marrow suppression, interstitial lung disease, paresthesias, and headaches (iii) Teratogen [57] Due to its hepatotoxic effects, concurrent use with methotrexate is not recommended. | Baseline: CBC and LFTs Follow-Up: both biweekly for the first six months, then bimonthly for the duration of treatment. |
| Mechanism of action | Indications | Administration | Side effects | Management |
|---------------------|-------------|----------------|-------------|------------|
| **Alkylating agents** | (i) Behcet’s disease (ii) Polyarteritis nodosa (iii) Wegener’s granulomatosis (iv) Mooren’s ulcer | IV Dose: starts at 1 g/m² and adjusted on response and side effects [51]. At the beginning of treatment, given biweekly. Discontinued if hematuria occurs, with urology consult indicated if hematuria persists beyond three weeks [51]. Course: once ocular quiescence is achieved, space treatment intervals to every 3–4 weeks continued for 1 year. | (i) Bone marrow suppression (ii) Hemorrhagic cystitis (iii) Secondary cancers (bladder, AML) (iv) Testicular atrophy (v) Ovarian suppression (vi) Known teratogen | Baseline: CBC, LFTs, UA Follow-Up: CBC and urinalysis are initially repeated weekly then spaced out to monthly intervals when blood counts are stabilized. |

(1) Cyclophosphamide
Cytotoxic properties are due to addition of an alkyl group to the guanine base of DNA and forming irreversible inter- and intrastrand DNA cross-links at guanine positions. This results in toxicity to rapidly-dividing cells (lymphocytes) and suppression of antibody production and delayed type hypersensitivity [58].

(i) Behcet’s disease (ii) Polyarteritis nodosa (iii) Wegener’s granulomatosis (iv) Mooren’s ulcer [59–64]

(2) Chlorambucil
Cytotoxic properties from addition of an alkyl group and forming DNA crosslinks [65].

(i) Sympathetic ophthalmia (ii) Behcet’s disease (iii) Serpiginous choroiditis [66, 67]

| **T-cell inhibitors/calcineurin inhibitors** | Oral Dose: two treatment algorithms. One starts at 0.1 mg/kg/day; maximum dosage 12 mg daily. The other uses short-term higher doses for 3–6 months [52]. Course: one year after ocular quiescence [47]. | (i) Heme/Onc myelosuppression, bone marrow aplasia, and secondary cancers (ii) Endocrine: male sterility, amenorrhea (iii) GI: hepatotoxicity (iv) CNS: seizures (v) Infectious: reactivation of latent herpes simplex virus [52, 68, 69]. | Baseline: CBC w. differential, LFT’s. Follow-Up: CBC initially repeated weekly, then spaced out to monthly intervals after stable dose. LFTs monthly. |

(1) Cyclosporine
Suppresses T lymphocyte activity and thus the immune response. Binds lymphocytic protein cyclophilin, which inhibits calcineurin. Since calcineurin normally activates interleukin-2 transcription, there is decreased T lymphocyte function [70].

Macrolide antibiotic, whose mechanism is similar to that of cyclosporine; both inhibit calcineurin and suppress T-cell signaling and IL-2 transcription [73].

(i) Behcet’s disease (ii) Sympathetic ophthalmia (iii) Sarcoidosis (iv) Birdshot retinochoroidopathy (v) VKH [71, 72]

Macrolide antibiotic, whose mechanism is similar to that of cyclosporine; both inhibit calcineurin and suppress T-cell signaling and IL-2 transcription [73].

(i) Oral (ii) IV Dose: 0.10–0.15 mg/kg/day. The more serious adverse effects are seen at higher doses [76–78]. | (i) Hypertension, gingival hyperplasia, lymphoma nephrotoxicity (ii) Myalgia, tremor, or paresthesias | Hypertension, nephron-toxicity, electrolyte abnormalities, anorexia, neurologic (insomnia, confusion, depression, catatonia, tremors, and seizures), non-Hodgkin’s lymphoma |

(2) Tacrolimus
| Oral Dose: initially 2.5 mg/kg/day, increased in increments of 50 mg; maximum 5 mg/kg/day [47]. Course: two years after ocular quiescence [47]. | | | Similar to cyclosporine. |
| Mechanism of action | Indications | Administration | Side effects | Management |
|---------------------|-------------|----------------|--------------|------------|
| (3) Rapamycin       | Inhibits cellular response to IL-2 and inhibits activation of B and T lymphocytes. | Oral; Dose: loading 6 mg; daily 2–6 mg/day [79]. | Elevated LFT’s, anemia, thrombocytopenia, hypercholesterolemia, nausea, abdominal pain, eczema, and increased risk of malignancy Markedly less nephrotoxic than other calcineurin inhibitors. | Similar to cyclosporine and tacrolimus |
| (1) Etanercept      | Targets TNF-α and TNF-β receptor, preventing molecules from binding, thus inactivating TNF. Thus it suppresses neutrophil migration and cytokine synthesis. | Subcutaneous; Dose: 25 mg twice a week, for two years. | Infection, increased risk for latent TB and hepatitis B reactivation, CNS demyelination, pancytopenia, congestive heart failure, and lymphoma [81, 82]. | Baseline: CBC, LFT’s, TB skin test, hepatitis B serologic testing Follow-Up: monthly CBC and LFTs [52, 83]. |
| (2) Infliximab      | Binds to and inhibits TNF-α (bound or circulating) [84]. | Intravenous; Dose: loading infusions weeks 0, 2, and 6; maintenance infusions every eight weeks [89]. | Infection (urinary tract, upper respiratory), GI (nausea, emesis), vasculitis, anemia, and thrombocytopenia [89–91]. | Baseline: CBC, LFT’s, TB skin test Follow-Up: monthly CBC and LFTs. |
| (3) Adalimumab      | Binds to and inhibits TNF-α [92]. | Subcutaneous; Dose: 40 mg every two weeks [93]. | Injection site reactions, infections (urinary tract, upper respiratory), headache and confusion, CNS demyelination, hepatotoxicity, congestive heart failure, and lymphoma [94, 95]. | Similar to infliximab. |
| (4) Daclizumab      | Binds to CD25, a subunit of the IL-2 receptor on T lymphocytes [96]. | Intravenous; Dose: 1 mg/kg every two weeks; maximum daily dose of 200 mg [100]. | Rash, lymphadenopathy, chest discomfort, and fever [101]. | Baseline: CBC, LFTs Follow-Up: repeat baseline labs prior to each infusion. |
| Mechanism of action | Indications | Administration | Side effects | Management |
|---------------------|-------------|----------------|--------------|------------|
| **(5) Rituximab**   | Binds to CD20, found on B lymphocytes. It thus suppresses B-cell differentiation, and decreased production of IgG and IgM [102]. | *(i) Wegener’s granulomatosis [19] (ii) Retinal vasculitis [20] (iii) Ocular cicatricial pemphigoid [22]* | *(i) Death from infection (Pneumocystis jiroveci, progressive multifocal leukoencephalopathy) (ii) Toxic epidermal necrolysis (iii) Pulmonary toxicity [103, 104] (iv) Severe infusion reaction, cytokine release syndrome, and acute renal failure [22].* | |
| **(6) Tocilizumab** | Blocks T/B-lymphocyte and monocyte IL-6 receptors, hindering its expression and proinflammatory effects. It increases Th1 cell specific regulatory binding protein of retinal photoreceptors, suggesting possible treatment of refractory uveitis associated with inflammatory or autoimmune processes [105]. | *(i) Rheumatoid and systemic juvenile idiopathic arthritis [23] (ii) Refractory uveitis [25]* | *(i) Common: infections, hypertension, headache, and transient increases in ALT [106] (ii) Rare: neutropenia, thrombocytopenia, GI perforations or gastritis, infections (TB, fungal) [107]* | |
| **(7) Gevokizumab** | Binds IL-1b and downregulates its activity. | Behcet’s | | |

**Other**
- **(1) Interferons**
  - Endogenous cytokines released in response to external pathogens.
  - Nonophthalmologic [28, 29]: *(i) Melanoma (ii) Hepatitis C (iii) Multiple sclerosis*
  - Ophthalmologic [30–33]: *(i) Behcet’s disease (IFN-α 2a) (ii) Multiple sclerosis uveitis (IFN-β 1a)*
  - Dose: IFN-α 2a given at 3–6 million international units, with frequency ranging from daily to three times weekly [108].
  - Course: maintain treatment after ocular inflammatory quiescence achieved for two years [7].
  - *(i) Common: fever, chills, myalgias, alopecia, and depression [109]. (ii) Interferon retinopathy Unlike other immunosuppressants and biologic agents, IFNs rarely cause infectious complications and are also not carcinogenic.*

- **(2) Anakinra**
  - IL-1 receptor antagonist; competitively inhibits binding of IL-1 to its receptor.
  - IL-1 has been found to have significance in systemic autoinflammatory diseases, where excessive IL-1 signaling will occur [36].

Baseline: CBC, LFTs, and thyroid function tests
Follow-Up: CBC and LFTs every four weeks; thyroid function tests every three months.
Table 3: Categories of vitritis drugs and what diseases they are indicated for.

| Drug                | Indications                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| **Antimetabolites** |                                                                             |
| Methotrexate        | Noninfectious chronic uveitis, ocular inflammation, ocular sarcoidosis       |
| Azathioprine        | Chronic uveitis, Behcet’s, choroidal neovascularization, ocular cicatricial pemphigoid, retinal vasculitis, serpiginous choroiditis |
| Mycophenolate mofetil | Chronic uveitis, noninfectious ocular inflammation, refractory uveitis, scleritis |
| Leflunomide         | Sarcoidosis                                                                 |
| **Alkylating agents** |                                                                             |
| Cyclophosphamide    | Refractory uveitis, noninfectious ocular inflammation, ANCA-associated vasculitides |
| Chlorambucil        | Serpiginous choroiditis, refractory uveitis, Behcet’s                        |
| **T-cell inhibitors/calcineurin inhibitors** |                                                                             |
| Cyclosporine        | Serpiginous choroidopathy, Behcet’s, scleritis, rheumatoid arthritis, noninfectious uveitis |
| Tacrolimus          | The above indications but usually in conjunction with systemic corticosteroids or adjunct immunosuppressants |
| Rapamycin           |                                                                             |
| **Biologic agents** |                                                                             |
| Etanercept          | Juvenile idiopathic arthritis, noninfectious uveitis, ocular inflammatory disease |
| Infliximab          | Refractory uveitis, childhood uveitis, Behcet’s                              |
| Adalimumab          | Refractory uveitis, ankylosing spondylitis, juvenile idiopathic arthritis   |
| Daclizumab          | Juvenile idiopathic arthritis, recalcitrant ocular inflammation, birdshot chorioretinopathy |
| Rituximab           | Primary Sjogren’s syndrome, thyroid eye disease, Wegener’s granulomatosis   |
| Tocilizumab         | Severe refractory posterior uveitis                                         |
| Gevokizumab         |                                                                             |
| **Other**           |                                                                             |
| Interferons         | Behcet’s, noninfectious uveitis                                             |
| Anakinra            | Behcet’s, refractory juvenile idiopathic disease                            |

Necrosis factor (TNF). It is able to bind with both high affinity and specificity to soluble TNFα or β, thus neutralizing the biological function of TNF, as well as modulating biological responses that TNF is responsible for inducing or regulating [11]. It is currently used with increasing frequency for treating several autoimmune diseases such as Behcet’s, juvenile idiopathic arthritis-associated uveitis, Vogt-Koyanagi-Harada (VKH) disease, and birdshot retinochoroidopathy [12-16]. A recent multicenter trial found it to be a useful treatment for patients with refractory uveitis, with a 10-week success rate of 68% [17].

Another recent retrospective analysis of 60 patients, the largest case series to date, showed a positive effect of adalimumab in 82% of these patients with different uveitis types, independent of additional systemic disease [11]. This study found that those who had been treated with infliximab and etanercept with insufficient response were effectively treated with adalimumab in 92% of cases. Another interesting finding was that patients pretreated with other TNF agents still had good results; thus, it is reasonable to switch to another TNF agent if the first was ineffective. In this study, no major infections or serious complications known to TNF inhibitors (demyelinating disease, reactivation of TB) occurred. This is a significant finding, as adalimumab may thus be a better option than infliximab, although follow-up was short and the study’s power would need to be increased in a further study.

Another prospective study evaluated the efficacy and outcomes of using adalimumab to treat uveitis associated with juvenile idiopathic arthritis [18]. Ocular symptom improvement was seen in 76% of cases, with anterior uveitis flare rate reduced after starting treatment. This study also confirmed a lack of serious sideeffects and infections and fewer hypersensitivity reactions than infliximab. Overall, this study concluded that adalimumab was a reasonable adjuvant therapy for treating uveitis.

3.2.2. Rituximab. Rituximab is an antibody that binds CD20, with many effects. Most commonly used in hematologic and autoimmune disorders, it has been found to be effective as a sole treatment for Wegener’s uveitis and retinal vasculitis [19, 20]. The value of rituximab in Behcet’s disease is yet to be determined, due to limited evidence [21]. In addition, it has also been used with intravenous IgG to treat ocular cicatricial pemphigoid [22].

3.2.3. Tocilizumab. Tocilizumab is a humanized antibody that binds both to IL-6 receptors, originally used for treating rheumatoid arthritis and systemic juvenile idiopathic arthritis [23]. IL-6 has a role in proliferation and differentiation
of T- and B-cells, with persistent production demonstrated in chronic inflammatory diseases. Although ophthalmologic usage is currently limited, patients with active posterior uveitis have been found to have elevated IL-6 levels in serum and intraocular, although levels were not specifically correlated with a clinical diagnosis [24].

In one retrospective study, tocilizumab was found to be efficacious in treating uveitis patients with cystoid macular edema that was refractory to intraocular steroids or other immunosuppressive therapies [25]. These patients were found to have complete resolution after six months of therapy and were also found to have no recurrence of inflammation at follow-up, suggesting that it is able to maintain disease remission. In another recent case study, a patient with severe refractory posterior uveitis improved, with decreasing levels of IL-6 after treatment [26].

3.2.4. Gevokizumab. IL-1β is an inflammatory cytokine produced in large amounts in Behcet's patients. Gevokizumab is a recombinant anti-IL-1β antibody, which modulates cytokine activity. It is a new therapy whose indications and efficacy are still being studied; a recent pilot study for patients with refractory Behcet's disease showed promising results, with only two infusions needed to render patients attack-free for several months [27]. Patients tolerated the infusions well, with no reported drug-related side effects. Treatment led to a rapid reduction in manifestations of intraocular inflammation, without the rebound attacks associated with discontinuation of corticosteroid use. This was thought to be in part due to accumulation of gevokizumab in ocular tissues, thus being able to sustain its therapeutic effect with an infrequent dosing interval.

3.3. Other

3.3.1. Interferons. Interferons (IFN) are endogenous cytokines, released in response to external pathogens. IFN-α 2a, IFN-α 2b, IFN-β 1a, and IFN-β 1b are the classes most commonly used in therapy. Interferons are commonly used to treat conditions ranging from malignancy (cutaneous melanoma), infection (hepatitis C), and inflammatory (multiple sclerosis) [28, 29]. As far as ophthalmologic uses, IFN-α 2a has successfully treated Behcet's disease, and IFN-β 1a reduced uveitis recurrences in multiple sclerosis patients [30–33]. In Behcet's disease, interferon demonstrated significant benefit by decreases in aphthous ulceration and the number of lesions [34]. Several studies consistently reported that many patients had durable remissions of ocular inflammatory disease after discontinuation.

3.3.2. Anakinra. Anakinra is an interleukin-1 receptor antagonist, which competitively inhibits IL-1 binding to its receptor. IL-1 has been found to have significance in systemic autoinflammatory diseases, where excessive IL-1 signaling will occur. It plays a key role in autoinflammatory diseases such as Muckle-Wells and neonatal onset multisystem inflammatory disease (NOMID), which are rare causes of uveitis in childhood [35]. It may in the future be used to treat refractory juvenile idiopathic and Behcet's disease, for which it is currently in phase III clinical trials [36].

4. Conclusion

Uveitis is a vision-threatening group of diseases that encompasses a variety of etiologies, which are either infectious or noninfectious. Both groups are commonly treated with steroids. Uveitis resulting from infection, however, focuses on eradicating the source with antibiotics or antivirals. Those of noninfectious origin may need additional immunosuppressive agents. These antimetabolites, cytotoxic agents, biologics, and immunomodulators can be used either alone or together, to control inflammation of the vitreous. As with any medication, especially immunosuppressants, side effects must be balanced with therapeutic benefit—a determination still in process for many drugs and indications. The complexities in investigating these therapies result from the innate heterogeneity of uveitis. Even with its difficulties, research on expanding indications for existing therapies and the discovery of new systemic agents continues to progress.

Conflict of Interests

The authors declare that there is no conflict of interests related to any topic in this paper.

References

[1] M. S.A. Suttorp-Schulten and A. Rothova, “The possible impact of uveitis in blindness: a literature survey,” British Journal of Ophthalmology, vol. 80, no. 9, pp. 844–848, 1996.
[2] J. B. Christoforidis, S. Chang, A. Jiang, J. Wang, and C. M. Cebulla, “Systemic treatment of vitreous inflammation,” Mediators of Inflammation, vol. 2012, Article ID 936721, 10 pages, 2012.
[3] D. A. Jabs and E. K. Akpek, “Immunosuppression for posterior uveitis,” Retina, vol. 25, no. 1, pp. 1–18, 2005.
[4] N. A. Sabrosa and C. Pavésio, “Treatment strategies in patients with posterior uveitis,” International Ophthalmology Clinics, vol. 40, no. 2, pp. 153–161, 2000.
[5] K. Kovacs, S. Wagley, M. T. Quirk et al., “Pharmacokinetic study of vitreous and serum concentrations of triamcinolone acetonide after posterior sub-Tenon’s injection,” American Journal of Ophthalmology, vol. 153, no. 5, pp. 939–948, 2012.
[6] C. Pavésio, M. Zierhut, K. Bairi, T. L. Comstock, and D. W. Usner, “Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis,” Ophthalmology, vol. 117, no. 3, pp. 567.e1–575.e1, 2010.
[7] K. Durrani, F. R. Zakka, M. Memon, S. S. Siddique, and C. S. Foster, “Systemic therapy with conventional and novel immunomodulatory agents for ocular inflammatory disease,” Survey of Ophthalmology, vol. 56, no. 6, pp. 474–510, 2011.
[8] K. Durrani, F. R. Zakka, M. Memon, S. S. Siddique, and C. S. Foster, “Systemic therapy with conventional and novel immunomodulatory agents for ocular inflammatory disease,” Survey of Ophthalmology, vol. 56, no. 6, pp. 474–510, 2011.
[9] R. P. Baughman and E. E. Lower, “Leflunomide for chronic sarcoidosis,” Sarcoidosis Vasculitis and Diffuse Lung Diseases, vol. 21, no. 1, pp. 43–48, 2004.
[10] C. Molina, C. Modesto, N. Martin-Begué, and C. Arnal, “Leflunomide, a valid and safe drug for the treatment of chronic
Mediators of Inflammation 9

anterior uveitis associated with juvenile idiopathic arthritis,” 
Clinical Rheumatology, 2013.

M. D. Becker, J. R. Smith, R. Max, and C. Fiehn, “Management of 
sight-threatening uveitis: new therapeutic options,” Drugs, vol. 65, no. 4, pp. 497–519, 2005.

B. Moustaq, T. Saeed, R. D. Situnayake, and P. I. Murray, “Adali-
mumab for sight-threatening uveitis in Behçet’s disease,” Eye, vol. 21, no. 6, pp. 824–825, 2007.

M. Diaz-Llopis, S. García-Delpech, D. Salom et al., “Adali-
mumab therapy for refractory uveitis: a pilot study,” Journal of 
Ocular Pharmacology and Therapeutics, vol. 24, no. 3, pp. 351–361, 2008.

J. P. Restrepo and M. P. Molina, “Successful treatment of severe 
nodular scleritis with adalimumab,” Clinical Rheumatology, vol. 29, no. 5, pp. 559–561, 2010.

L. B. Vazquez-Cobian, T. Flynn, and T. J. A. Lehman, “Adali-
mumab therapy for childhood uveitis,” Journal of Pediatrics, vol. 149, no. 4, pp. 572–575, 2006.

P. Tynjälä, K. Kotaniemi, P. Lindahl et al., “Adalimumab in 
Behcet’s disease: results of a multicentre, open-
label, prospective trial,” British Journal of Ophthalmology, vol. 97, no. 4, pp. 481–486, 2013.

A. Magli, R. Forte, P. Navarro et al., “Adalimumab for juvenile 
idiopathic arthritis-associated uveitis,” Graefes Archive for 
Clinical and Experimental Ophthalmology, vol. 251, no. 6, pp. 1601–1606, 2013.

F. Davatchi, H. Shams, M. Rezaipoor et al., “Rituximab in 
intratable ocular lesions of Behçet’s disease; randomized single-blind control study (pilot study),” International Journal of 
Rheumatic Diseases, vol. 13, no. 3, pp. 246–252, 2010.

S. R. J. Taylor, A. D. Salama, L. Joshi, C. D. Pusey, and S. L. 
Lightman, “Rituximab is effective in the treatment of refractory 
ophthalmic Wegener’s granulomatosis,” Arthritis and Rheu-
matism, vol. 60, no. 5, pp. 1540–1547, 2009.

C. S. Foster, P. Y. Chang, and A. R. Ahmed, “Combination of rit-
uximab and intravenous immunoglobulin for recalcitrant ocu-
ar cicatricial pemphigoid. A preliminary report,” Ophthalmology, vol. 117, no. 5, pp. 861–869, 2010.

A. Bermudez, F. Marco, E. Conde, E. Mazo, M. Recio, and A. 
Zubizarreta, “Fatal visceral varicella-zoster infection following 
rituximab and chemotherapy treatment in a patient with fol-
locular lymphoma,” Haematologica, vol. 85, no. 8, pp. 894–895, 2000.

G. Jones, A. Sebja, J. Gu et al., “Comparison of tocilizumab 
monotherapy versus methotrexate monotherapy in patients 
with moderate to severe rheumatoid arthritis: the AMBITION 
study,” Annals of the Rheumatic Diseases, vol. 69, no. 1, pp. 88–96, 2010.

V. L. Perez, G. N. Papaliodis, D. Chu, F. Anzaar, W. Christen, 
and C. S. Foster, “Elevated levels of interleukin 6 in the vitreous 
fluid of patients with pars planitis and posterior uveitis: the 
Massachusetts eye & ear experience and review of previous 
studies,” Ocular Immunology and Inflammation, vol. 12, no. 3, pp. 193–201, 2004.

A. Adán, M. Mesquida, V. Llorenç et al., “Tocilizumab treatment 
for refractory uveitis-related cystoid macular edema,” Graefes 
Archive for Clinical and Experimental Ophthalmology, 2013.

T. Hirano, N. Ohguro, S. Kohki et al., “A case of Behçet’s disease 
treated with a humanized anti-interleukin-6 receptor antibody, 
tocilizumab,” Modern Rheumatology, vol. 22, pp. 298–302, 2012.

A. Gül, I. Tugal-Tutkun, C. A. Dinarello et al., “Interleukin-1β-
regulating antibody XOMA 052 (gevokizumab) in the treatment of 
acute exacerbations of resistant uveitis of Behçet’s disease: an 
open-label pilot study,” Annals of the Rheumatic Diseases, vol. 71, no. 4, pp. 563–566, 2012.

F. Hayden, “Antiviral agents (non-retroviral),” in Goodman & 
Gilman’s the Pharmacological Basis of Therapeutics, L. S. 
Goodman, A. Gilman, L. L. Brunton, J. S. Lazo, and K. L. Parker, 
Eds., pp. 1243–1272, McGraw-Hill, New York, NY, USA, 2006.

S. Mocellin, S. Pasquali, C. R. Rossi, and D. Nitti, “Interferon 
alpha adjuvant therapy in patients with high-risk melanoma: 
a systematic review and meta-analysis,” Journal of the National 
Cancer Institute, vol. 102, no. 7, pp. 493–501, 2010.

E. Alpsoy, C. Durusoy, E. Yilmaz et al., “Interferon alfa-2a in the 
treatment of Behçet disease: a randomized placebo-controlled 
and double-blind study,” Archives of Dermatology, vol. 138, no. 4, pp. 467–471, 2002.

I. Kötter, R. Vonthien, M. Zierhut et al., “Differential efficacy of 
human recombinant interferon-α2a on ocular and extracranial 
manifestations of Behçet disease: results of an open 4-center 
trial,” Seminars in Arthritis and Rheumatism, vol. 33, no. 5, pp. 
311–319, 2004.

F. Mackensen, R. Max, and M. D. Becker, “Interferons and 
their potential in the treatment of ocular inflammation,” Clinical 
Ophthalmology, vol. 3, no. 1, pp. 559–566, 2009.

M. D. Becker, A. Heiligenhaus, T. Huddé et al., “Interferon as a 
treatment for uveitis associated with multiple sclerosis,” British 
Journal of Ophthalmology, vol. 89, no. 10, pp. 1254–1257, 2005.

N. Warde, “Therapy: Behçet uveitis: good results for IFN-α-2a,” 
Nature Reviews Rheumatology, vol. 6, no. 8, article 437, 2010.

A. Tarabishy, A. Hise, and E. Traboulsi, “Ocular manifestations of 
the autoinflammatory syndromes,” Ophthalmic Genetics, vol. 33, no. 4, pp. 179–186, 2012.

D. Saadoun, B. Bodaghi, B. Bienvenu et al., “Biotherapies in 
inflammatory ocular disorders: interferons, immunoglobulins, 
monoclonal antibodies,” Autoimmunity Reviews, vol. 12, no. 7, pp. 774–783, 2013.

A. Johnston, J. E. Gujdonssson, H. Sigmundsdottir, B. Runar 
Ludviksson, and H. Valdimarsson, “The anti-inflammatory 
action of methotrexate is not mediated by lymphocyte apop-
tosis, but by the suppression of activation and adhesion 
molecules,” Clinical Immunology, vol. 114, no. 2, pp. 154–163, 2005.

F. F. Lee and C. S. Foster, “Pharmacotherapy of uveitis,” Expert 
Opinion on Pharmacotherapy, vol. 11, no. 7, pp. 1135–1146, 2010.

M. E. Weinblatt, “Toxicity of low dose methotrexate in rheuma-
toid arthritis,” Journal of Rheumatology, vol. 12, supplement 12, pp. 35–39, 1985.

D. BenEzra and E. Cohen, “Cataract surgery in children with 
chronic uveitis,” Ophthalmology, vol. 107, no. 7, pp. 1255–1260, 2000.

G. L. C. Chan, D. M. Canafax, and C. A. Johnson, “The therapeu-
ctic use of azathioprine in renal transplantation,” Pharma-
cotherapy, vol. 7, no. 5, pp. 165–177, 1987.

P. L. Hooper and H. J. Kaplan, “Triple agent immunosuppres-
sion in serpiginous choroiditis,” Ophthalmology, vol. 98, no. 6, pp. 944–952, 1991.
[43] S. S. Michel, A. Ekong, S. Baltazis, and C. S. Foster, "Multifocal chorioretinitis and panuveitis: immunomodulatory therapy," Ophthalmology, vol. 109, no. 2, pp. 378–383, 2002.

[44] V. P. J. Saw, J. K. G. Dart, S. Rauz et al., "Immunosuppressive therapy for ocular mucous membrane pemphigoid. Strategies and outcomes," Ophthalmology, vol. 115, no. 2, pp. 253.e1–261.e1, 2008.

[45] C. S. Foster and A. T. Vitale, "Immunosuppressive chemotherapy," in Diagnosis and Treatment of Uveitis, C. S. Foster and A. T. Vitale, Eds., WB Saunders, Philadelphia, PA, USA, 2002.

[46] J. K. Whisnant and J. Pelkey, "Rheumatoid arthritis: treatment considerations," in 50 Years of Uveitis, S. B. Smolin and P. Emery, Eds., Saunders, Philadelphia, PA, USA, 2002.

[47] A. C. Allison and E. M. Eugui, "Immunosuppressive and other agents," in 50 Years of Uveitis, S. B. Smolin and P. Emery, Eds., Saunders, Philadelphia, PA, USA, 2002.

[48] R. Voisard, S. Viola, V. Kaspar et al., "Effects of mycophenolate mofetil on key pattern of coronary restenosis: a cascade of in vitro and ex vivo models," BMC Cardiovascular Disorders, vol. 5, article 9, 2005.

[49] L. Sobrin, W. Christen, and C. S. Foster, "Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis," Ophthalmology, vol. 115, no. 8, pp. 1416.e1–1421.e1, 2008.

[50] D. A. Jabs, J. T. Rosenbaum, C. S. Foster et al., "Guidelines for the use of immunosuppressive drugs in patients with uveal inflammatory disorders: recommendations of an expert panel," American Journal of Ophthalmology, vol. 130, no. 4, pp. 492–513, 2000.

[51] R. I. Fox, M. L. Herrmann, C. G. Frangou et al., "Mechanism of action for leflunomide in rheumatoid arthritis," Clinical Immunology, vol. 93, no. 3, pp. 198–208, 1999.

[52] J. Tedesco Silva H. and R. E. Morris, "Leflunomide and malononitriloamides," Expert Opinion on Investigational Drugs, vol. 6, no. 1, pp. 51–64, 1997.

[53] Anon, Leflunomide ADIS Re&D Insight ADIS International, 1998.

[54] J. S. Smolen, P. Emery, J. R. Kalden et al., "The efficacy of leflunomide monotherapy in rheumatoid arthritis: towards the goals of disease modifying antirheumatic drug therapy," Journal of Rheumatology, vol. 31, no. 7, pp. 13–20, 2004.

[55] H. M. Roussel, Summary of Product Characteristics For Arava, Hoechst Marion Roussel, Uxbridge, UK, 1999.

[56] S. Cohen, G. W. Cannon, M. Schiff et al., "Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate," Arthritis and Rheumatism, vol. 44, no. 9, pp. 1984–1992, 2001.

[57] A. S. Fauci, S. M. Wolf, and J. S. Johnson, "Effect of cyclophosphamide upon the immune response in Wegener's granulomatosis," The New England Journal of Medicine, vol. 285, no. 27, pp. 1493–1496, 1971.

[58] C. E. Buckley III and J. P. Gills Jr., "Cyclophosphamide therapy of Behçet's disease," Journal of Allergy, vol. 43, no. 5, pp. 273–283, 1969.

[59] C. S. Foster, L. A. Wilson, and M. B. Ekins, "Immunosuppressive therapy for progressive ocular cicatricial pemphigoid," Ophthalmology, vol. 89, no. 4, pp. 340–353, 1982.

[60] W. M. Fosdick, J. L. Parsons, and D. F. Hill, "Long-term cyclophosphamide therapy in rheumatoid arthritis," Arthritis and Rheumatism, vol. 11, no. 2, pp. 151–161, 1968.

[61] R. Brubaker, R. L. Font, and E. M. Shepherd, "Granulomatous sclerouveitis. Regression of ocular lesions with cyclophosphamide and prednisone," Archives of Ophthalmology, vol. 86, no. 5, pp. 517–524, 1971.

[62] A. S. Fauci, J. L. Doppman, and S. M. Wolff, "Cyclophosphamide-induced remissions in advanced panarteritis nodosa," American Journal of Medicine, vol. 64, no. 5, pp. 890–894, 1978.

[63] T. Hoang-Xuan, C. S. Foster, and B. A. Rice, "Scleritis in relapsing polychondritis. Response to therapy," Ophthalmology, vol. 97, no. 7, pp. 892–898, 1990.

[64] B. A. Chaibner, P. C. Amrein, B. Drucker et al., "Antineoplastic agents," in Goodman & Gilman's the Pharmacological Basis of Therapeutics, L. S. Goodman, A. Gilman, L. B. Brunton, J. S. Lazo, and K. L. Parker, Eds., pp. 1315–1404, McGraw-Hill, New York, NY, USA, 2006.

[65] E. Misericocchi, S. Baltazis, A. Ekong, M. Roque, and C. S. Foster, "Efficacy and safety of chlorambucil in intractable noninfectious uveitis: the Massachusetts eye and ear infirmary experience," Ophthalmology, vol. 109, no. 1, pp. 137–142, 2002.

[66] A. B. Mudun, A. Ergen, Ş. U. Ipıcıoglu, E. Y. Burumcek, Y. Durlu, and M. O. Arslan, "Short-term chlorambucil for refractory uveitis in Behçet's disease," Ocular Immunology and Inflammation, vol. 9, no. 4, pp. 219–229, 2001.

[67] G. W. Cannon, C. G. Jackson, and C. O. Samuelson, "Chlorambucil therapy in rheumatoid arthritis: clinical experience in 28 patients and literature review," Seminars in Arthritis and Rheumatism, vol. 15, no. 2, pp. 106–118, 1985.

[68] K. F. Tabbara, "Chlorambucil in Behçet's disease. A reappraisal," Ophthalmology, vol. 90, no. 8, pp. 906–908, 1983.

[69] D. A. Gerber, C. A. Bonham, and A. W. Thomson, "Immunosuppressive agents: recent developments in molecular action and clinical application," Transplantation Proceedings, vol. 30, no. 4, pp. 1573–1579, 1998.

[70] A. G. Palestine, R. B. Nussenblatt, and M. Gelato, "Therapy for human autoimmune uveitis with low-dose cyclosporine plus bromocriptine," Transplantation Proceedings, vol. 20, no. 3, supplement 4, pp. 131–135, 1988.

[71] A. T. Vitale, A. Rodriguez, and C. S. Foster, "Low-dose cyclosporine therapy in the treatment of birdshot retinochoroidopathy," Ophthalmology, vol. 101, no. 5, pp. 822–831, 1994.

[72] J. Liu, J. D. Farmer Jr., W. S. Lane, J. Friedman, I. Weissman, and S. L. Schreiber, "Calcineurin is a common target of cyclophillin-cyclosporin A and FKBP-FK506 complexes," Cell, vol. 66, no. 4, pp. 807–815, 1991.

[73] A. J. Kilmartin, J. V. Forrester, and A. D. Dick, "Tacrolimus (FK506) in failed cyclosporin A therapy in endogenous posterior uveitis," Ocular Immunology and Inflammation, vol. 6, no. 2, pp. 101–109, 1998.

[74] C. M. L. Sloper, R. J. Powell, and H. S. Dua, "Tacrolimus (FK506) in the treatment of posterior uveitis refractory to cyclosporine," Ophthalmology, vol. 106, no. 4, pp. 723–728, 1999.

[75] M. Naesens, D. R. J. Kuypers, and M. Sarwal, "Calcineurin inhibitor nephrotoxicity," Clinical Journal of the American Society of Nephrology, vol. 4, no. 2, pp. 481–508, 2009.

[76] Y. Miwa, T. Isozaki, K. Wakabayashi et al., "Tacrolimus-induced lung injury in a rheumatoid arthritis patient with interstitial pneumonitis," Modern Rheumatology, vol. 18, no. 2, pp. 208–211, 2008.
Mediators of Inflammation

[78] M. M. O’Donnell, J. P. Williams, R. Weinrieb, and L. Denysenko, “Catastolic mutism after liver transplant rapidly reversed with lorazepam,” General Hospital Psychiatry, vol. 29, no. 3, pp. 280–281, 2007.

[79] V. A. Shanmuganathan, E. M. Casely, D. Raj et al., “The efficacy of sirolimus in the treatment of patients with refractory uveitis,” British Journal of Ophthalmology, vol. 89, no. 6, pp. 666–669, 2005.

[80] B. N. Phillips and K. J. Wroblewski, “A retrospective review of oral low-dose sirolimus (rapamycin) for the treatment of active uveitis,” Journal of Ophthalmic Inflammation and Infection, vol. 1, no. 1, pp. 29–34, 2011.

[81] S. B. Desai and D. E. Furst, “Problems encountered during anti-tumour necrosis factor therapy,” Best Practice and Research, vol. 20, no. 4, pp. 757–790, 2006.

[82] N. Scheinfeld, “A comprehensive review and evaluation of the site effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab,” Journal of Dermatological Treatment, vol. 15, no. 5, pp. 280–294, 2004.

[83] J. Lin, D. Ziring, S. Desai et al., “TNFα blockade in human diseases: an overview of efficacy and safety,” Clinical Immunology, vol. 126, no. 1, pp. 13–30, 2008.

[84] L. H. Calabrese, “Molecular differences in anticytokine therapies,” Clinical and Experimental Rheumatology, vol. 21, no. 2, pp. 241–248, 2003.

[85] B. Bodaghi, E. Bui Quoc, B. Wechsler et al., “Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors,” Annals of the Rheumatic Diseases, vol. 64, no. 6, pp. 962–964, 2005.

[86] R. P. Baughman, D. A. Bradley, and E. E. Lower, “Infliximab in chronic ocular inflammation,” International Journal of Clinical Pharmacology and Therapeutics, vol. 43, no. 1, pp. 7–11, 2005.

[87] P. Kahn, M. Weiss, L. F. Imundo, and D. M. Levy, “Favorable response to high-dose infliximab for refractory childhood uveitis,” Ophthalmology, vol. 113, no. 5, pp. 864.e2–864.e2, 2006.

[88] L. Niccoli, C. Nannini, M. Benucci et al., “Long-term efficacy of infliximab in refractory posterior uveitis of Behçet’s disease: a 24-month follow-up study,” Rheumatology, vol. 46, no. 7, pp. 1161–1164, 2007.

[89] E. B. Suhler, J. R. Smith, T. R. Giles et al., “Infliximab therapy for refractory uveitis: 2-year results of a prospective trial,” Archives of Ophthalmology, vol. 127, no. 6, pp. 819–822, 2009.

[90] J. Braun, J. Brandt, J. Listing et al., “Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial,” Arthritis and Rheumatism, vol. 48, no. 8, pp. 2224–2233, 2003.

[91] J. J. Gómez-Reino, L. Carmona, V. Rodriguez Valverde, E. M. Mola, and M. D. Montero, “Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report,” Arthritis and Rheumatism, vol. 48, no. 8, pp. 2122–2127, 2003.

[92] Z. Kaymakcalan, P. Sakorafas, S. Bose et al., “Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor,” Clinical Immunology, vol. 131, no. 2, pp. 308–316, 2009.

[93] M. Rudwaleit, E. Rödevand, P. Holck et al., “Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study,” Annals of the Rheumatic Diseases, vol. 68, no. 5, pp. 696–701, 2009.

[94] J. A. Singh, G. A. Wells, R. Christensen et al., “Adverse effects of biologics: a network meta-analysis and Cochrane overview,” Cochrane Database of Systematic Reviews, vol. 2, Article ID CD008794, 2011.

[95] A. Alonso-Ruiz, J. I. Pijoan, E. Ansutegui, A. Urkaregi, M. Calabozo, and A. Quintana, “Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety,” BMC Musculoskeletal Disorders, vol. 9, article 52, 2008.

[96] H. Yang, J. Wang, J. Du et al., “Structural basis of immunosuppression by the therapeutic antibody daclizumab,” Cell Research, vol. 20, no. 12, pp. 1361–1371, 2010.

[97] L. Sobrin, J. J. Huang, W. Christen, C. Kalkala, P. Choopong, and C. S. Foster, “Daclizumab for treatment of birdshot chorioretinopathy,” Archives of Ophthalmology, vol. 126, no. 2, pp. 186–191, 2008.

[98] H. N. Sen, G. Levy-Clarke, L. J. Faia et al., “High-dose daclizumab for the treatment of juvenile idiopathic arthritis-associated active anterior uveitis,” American Journal of Ophthalmology, vol. 148, no. 5, pp. 696.e1–703.e1, 2009.

[99] M. Gallagher, K. Quinones, R. A. Cervantes-Castañeda, T. Yilmaz, and C. S. Foster, “Biological response modifier therapy for refractory childhood uveitis,” British Journal of Ophthalmology, vol. 91, no. 10, pp. 1341–1344, 2007.

[100] P. Bhat, R. A. Castañeda-Cervantes, P. P. Doctor, and C. S. Foster, “Intravenous daclizumab for recalcitrant ocular inflammatory disease,” Graefes Archive for Clinical and Experimental Ophthalmology, vol. 247, no. 5, pp. 687–692, 2009.

[101] M. A. Rojas, N. G. Carlson, T. L. Miller, and J. W. Rose, “Long-term daclizumab therapy in relapsing-remitting multiple sclerosis,” Therapeutic Advances in Neurological Disorders, vol. 2, no. 5, pp. 291–297, 2009.

[102] L. Lim, E. B. Suhler, and J. R. Smith, “Biologic therapies for inflammatory eye disease,” Clinical and Experimental Ophthalmology, vol. 34, no. 4, pp. 365–374, 2006.

[103] P. Quartier, O. Tournilhac, C. Archimbaud et al., “Enteroviral meningencephalitis after anti-CD20 (rituximab) treatment,” Clinical Infectious Diseases, vol. 36, no. 3, pp. e47–e49, 2003.

[104] Genentech, Products-Product Information-Immunology—Rituxan RA Full Prescribing Information, 2007.

[105] H. Haruta, N. Ohguro, M. Fujimoto et al., “Blockade of interleukin-6 signaling suppresses not only Th1 but also interphotorceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis,” Investigative Ophthalmology & Visual Science, vol. 52, no. 6, pp. 3264–3271, 2011.

[106] V. Dinnendahl and U. Fricke, Arzneistoff-Profil, vol. 4, Givi Pharmazeutischer, Eschborn, Germany, 32 edition, 2010.

[107] S. Dhillon, V. Oldfield, and G. L. Plosker, “Tocilizumab: a review of its use in the management of rheumatoid arthritis,” Drugs, vol. 69, no. 5, pp. 609–632, 2009.

[108] C. M. E. Deuter, M. Zierhut, A. Möhle, R. Vonthein, N. Stöbiger, and I. Köttler, “Long-term remission after cessation of interferon-α treatment in patients with severe uveitis due to Behçet’s disease,” Arthritis and Rheumatism, vol. 62, no. 9, pp. 2796–2805, 2010.

[109] I. Köttler, I. Gündaydin, M. Zierhut, and N. Stöbiger, “The use of interferon alpha in Behçet disease: review of the literature,” Seminars in Arthritis and Rheumatism, vol. 33, no. 5, pp. 320–335, 2004.