Published in final edited form as:

Expert Opin Emerg Drugs. 2011 June ; 16(2): 309–322. doi:10.1517/14728214.2011.537824.

Emerging Drugs for Uveitis

Theresa Larson, MD, Robert B. Nussenblatt, MD, MPH, and H. Nida Sen, MD, MHSc*

National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

Importance of the Field—Uveitis is a challenging disease covering both infectious and noninfectious conditions. The current treatment strategies are hampered by the paucity of randomized controlled trials (RCTs) and few trials comparing efficacy of different agents.

Areas Covered in this Review—This review describes the current and future treatments of uveitis. A literature search was performed in PUBMED from 1965 to 2010 on drugs treating ocular inflammation with emphasis placed on more recent, larger studies.

What the Reader Will Gain—Readers should gain a basic understanding of current treatment strategies beginning with corticosteroids and transitioning to steroid sparing agents. Steroid sparing agents include the antimetabolites which include methotrexate, azathioprine, and mycophenolate mofetil; the calcineurin inhibitors which include cyclosporine, tacrolimus; alkylating agents which include cyclophosphamide and chlorambucil; and biologics which include the TNF- α inhibitors infliximab, adalimumab, and etanercept; daclizumab, interferon α 2a, and rituximab.

Take Home Message—Newer agents are typically formulated from existing drugs or developed based on new advances in immunology. Future treatment will require a better understanding of the mechanisms involved in autoimmune diseases and better delivery systems in order to provide targeted treatment with minimal side effects.

Keywords

Uveitis; Autoimmune; Inflammation; Immunosuppression; Biologics

1. Background

Uveitis encompasses diverse diseases both in etiology and anatomic location within the eye ranging from the anterior uveitis managed with topical prednisolone to severe sight threatening episodes seen in Behcet's disease requiring aggressive systemic immunosuppression. The term describes any inflammation within the eye from the uvea which comprises the iris, ciliary body, and choroid as well as the sclera, retina, vitreous, and optic nerve. It describes both infectious and noninfectious conditions which can be associated with systemic disease or limited to the eye. Infectious etiologies include toxoplasmosis, syphilis, bartonella, and Lyme disease to noninfectious etiologies such as sarcoidosis which have systemic implications. Uveitis can also be idiopathic and limited only to the eye as in birdshot retinochoroiditis, one of the entities known as white dot syndromes. The current classification scheme used to describe uveitis is from the

*corresponding author: senh@nei.nih.gov.

Declaration of interest

None of the authors have any conflict of interest in the materials mentioned in the manuscript.

International Uveitis Study Group which is based on an anatomic framework: anterior, intermediate, posterior, and panuveitis.¹

The most common form of uveitis in the western countries is acute anterior uveitis (AAU).² It is most commonly associated with HLA-B27 which has important systemic, clinical, and prognostic features. HLA-B27 AAU can be associated with ocular inflammation alone or in association with systemic disease. Systemic disease associations include ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, psoriatic arthropathy, and undifferentiated spondylarthropathy. HLA-B27 AAU has characteristic clinical features including male preponderance, unilateral alternating acute onset, a non-granulomatous appearance, and frequent recurrences whereas HLA-B27 negative AAU has an equivalent male to female onset, bilateral chronic course, and more frequent granulomatous appearance.³ In general, AAU has the best visual prognosis of the types of uveitis; however, HLA-B27 AAU is associated with greater use of steroids and immunosuppressive therapy as well as more ocular complications compared to HLA-B27 negative AAU.⁴

2. Medical Need

Untreated uveitis can lead to serious sequelae such as permanent vision loss. It accounts for approximately 10% of visual handicap in the Western World or 30,000 new cases of blindness at an incidence of 20–52 cases per 100,000 person-years.^{5–7} It occurs more commonly in women. Previous studies have found the younger, working age group of 25–44 year olds most frequently affected, however, a more recent study from Northern California showed a higher incidence in the elderly population over 65 years old.⁷

In a retrospective review of uveitis patients, 35% exhibited blindness or visual impairment (defined as worse than 20/200 or 20/60). Cystoid macular edema (CME) was the most frequent cause of blindness or visual impairment and complications from uveitis such as cataract and glaucoma occurred in more than one-half of patients. Panuveitis was the anatomical diagnosis with the worst prognosis⁸

The economic costs from uveitis are also significant. Although there are no studies primarily addressing the direct and indirect cost among uveitis patients, once vision drops below 20/40, a person's ability is affected in the workplace and since approximately 70–90% of those with uveitis are between 20–60 years of age, uveitis is affecting patients during their most economically productive years. No studies have been performed on the cost of blindness secondary to uveitis, however, if the assumption is made that 6% of the population is blinded by uveitis, then the total annual cost for the United States is about 242.6 million dollars.⁹

Despite the potentially blinding disease and huge economic impact, few randomized controlled trials have been performed for uveitis. There are very few studies comparing efficacy between agents in treating ocular inflammation. Given the prevalence of the disease, such studies inevitably require multi-institution networks. Most studies performed are small retrospective case series based on experience with a single agent and most often include a heterogeneous group of patients with more than one specific disease diagnosis. Within uveitis, patients with varying diagnoses may behave very differently and the definition of success may vary thus making these studies even harder to interpret.

3. Existing Treatment

3.1 Corticosteroids

Corticosteroids are the mainstay of therapy in uveitis. They come in multiple formulations including systemic treatment with oral prednisone or intravenous methylprednisolone

sodium succinate (Solu-Medrol; Pharmacia and Upjohn, Peapack, New Jersey). Local treatments include topical preparations such as prednisolone acetate or difluprednate, periocular treatment, intravitreally with triamcinolone or Triescence, or ocular implants all of which offer the benefit of avoiding systemic complications. Indications for different formulations depend on the site and activity of the uveitis.

The introduction of oral corticosteroids revolutionized the treatment of inflammatory disorders with diseases such as rheumatoid arthritis. They work on multiple signaling mechanisms to inhibit inflammation but in the process have many adverse effects. They have been used in ocular inflammatory disorders since the 1950s and through unknown mechanisms are thought to stabilize the blood-retinal barrier.¹⁰ In treating eyes with sarcoid uveitis, visual outcomes are superior with corticosteroid use.¹¹ For vision threatening uveitis, steroids are typically started at 1 mg/kg for up to a month or until the disease is under control.¹² For acute flares with sight threatening inflammatory disease such as Behcet's retinitis, treatment with high dose i.v pulse methylprednisone may be helpful.¹³ Oral corticosteroid use is limited secondary to Cushingoid effects, mood changes, diabetes, hypertension, and fluid retention. In children, steroids suppress the adrenal system and can cause growth retardation. Ocular side effects include cataract and glaucoma.

Topical preparations work best for anterior uveitis and episcleritis with limited efficacy for the posterior segment of the eye. Their side effects are typically limited to local effects on the eye and include intraocular pressure elevation and cataract.^{14–15} Periocular steroids offer the benefit of higher, local, sustained drug to the eye with greater posterior segment penetration, making them effective for intermediate uveitis, uveitic macular edema, and posterior uveitis. Typically, periocular steroids are administered as 40 mg triamcinolone through the posterior subtenon or orbital floor or alternatively as 40 mg methylprednisolone through the orbital floor. In a series of patients with intermediate uveitis, 67% responded to periocular steroids with a 2 line increase in vision. Side effects are similar to topical formulations with approximately 30% of patients having a rise in intraocular pressure as well as cataract and very rarely inadvertent ocular penetration.¹⁶ Intravitreal triamcinolone (IVTA) offers the most direct route to the posterior segment and thus potentially greater efficacy for uveitic macular edema and posterior uveitis.¹⁷ It is administered intravitreally as 1–4 mg in 0.1 ml. For patients with uveitic CME not responding to oral steroids, periocular injections, and immunosuppressive agents, IVTA can be useful with resultant vision improvement. Effects are typically greater if CME is present less than 12 months.¹⁸ However, the effects can be short-lived as the half-lives of drugs in the vitreous are limited. Young et al., showed in a small series that although all patients had resolution of uveitis related CME there was recurrence in majority of patients by 6 months.¹⁰ Ocular complications include elevated intraocular pressure, cataract, sterile endophthalmitis, and infectious endophthalmitis.^{19–21}

Steroid implants offer the benefit of sustained corticosteroid delivery to the eye while avoiding systemic complications of other therapies. The fluocinolone acetonide implant (RetisertTM, Baush and Lomb, Rochester, NY) was developed to deliver corticosteroid for up to 30 months and is currently approved in the U.S. as a 0.59 mg fluocinolone acetonide implant (FA) for chronic non-infectious posterior uveitis. In the multicenter randomized study comparing the 0.59 mg to 2.1 mg fluocinolone acetonide implant, approximately 80% of subjects experienced a 3 year recurrence free period of uveitis with the 0.59 mg FA implant. There was improvement in both vision and reduction in CME in implanted eyes vs. non-implanted fellow eyes. However, 78% required IOP lowering drops, 36% required glaucoma surgery, nearly all eyes required cataract surgery, and there was one case of endophthalmitis.²² Vitreous band formation has also been reported.²³ The implant is currently

being compared to systemic therapy for intermediate uveitis, posterior uveitis, or panuveitis in The Multicenter Uveitis Steroid Treatment Trial (MUST Trial).²⁴

Another implant recently approved by the FDA for the treatment of noninfectious posterior uveitis is a dexamethasone intravitreal implant (Ozurdex™, Allergan, Inc., Irvine, CA). It is a 0.7 mg biodegradable implant that delivers extended release of dexamethasone through the Novadur solid polymer delivery system. It is given intravitreally via an injector in an office-based procedure. This is in contrast to the FA implant which requires surgical placement in the operating room.²⁵ The efficacy of Ozurdex for noninfectious intermediate or posterior uveitis was assessed in a 26-week, multicenter, double-masked, randomized clinical trial in which 77 patients received the drug and 76 patients received sham injections. Patients achieving a vitreous haze score of 0 (no inflammation) at 8 weeks was statistically significant in the Ozurdex treated group (47% versus 12%) and patients achieving a 3 line improvement in best corrected vision was 43% in the treated group versus 7% in the sham group. The most common ocular complications included intraocular pressure elevation in 25% and conjunctival hemorrhage in 22%. Cataract occurred in 5% (Ozurdex package insert, http://www.allergan.com/assets/pdf/ozurdex_pi.pdf).

Corticosteroid sparing agents are indicated when inflammation requires high dose steroids for control of ocular inflammation for more than 1 month (>60 mg or less based on the weight of individual dosed 1 mg/kg), chronic doses greater than 7.5 mg., or side effects requiring discontinuation of steroids.¹² Patients are typically transitioned to steroid sparing therapy and the steroid is slowly tapered once the ocular inflammation is quiet. There are several classes of agents including antimetabolites, T-cell inhibitors, alkylating agents, and biologic agents (see Table 1).

3.2 Antimetabolites

Antimetabolites refer to a class of drugs which inhibit nucleic acid synthesis and thus inhibit cell proliferation.²⁶ Drugs commonly used in the treatment of uveitis in this class include methotrexate, azathioprine, and mycophenolate mofetil. Methotrexate was first introduced in 1948 as an antineoplastic agent.²⁷ It is a folate analogue and works by inhibiting dihydrofolate reductase which is involved in the synthesis of thymidilate and purine nucleotide synthesis, resulting in the inhibition of rapidly dividing cells such as lymphocytes. It was approved by the FDA for the treatment of rheumatoid arthritis in 1988 and first used in ocular inflammatory disease in the 1965.²⁸ It is dosed at 7.5 mg to 25 mg once per week in conjunction with folic acid. When given orally up to 35% is metabolized by intestinal flora but when given parenterally, there is 100% absorption.¹² The most serious side effects of methotrexate include hepatotoxicity, cytopenias, and interstitial pneumonitis. Monitoring of liver function tests is required during treatment. It is teratogenic and thus contraindicated in pregnancy.

Methotrexate is a widely used agent for ocular inflammation because of its ease of administration and long track record. In the retrospective Systemic Immunosuppression for Eye Disease Cohort Study (SITE) which included 384 patients, methotrexate was found to be moderately effective with an overall success of 66% at 12 months for sustained control and 58.4% for corticosteroid sparing control (≤ 10 mg). From the data, it appeared to be more successful for treatment of anterior disease; however, the authors caution that this observed effect may be related to the severity of the disease. It was found to be safe with just 16% patients discontinued because of side effects which were reversible.²⁹ Other studies have looked at smaller cohorts of patients and also found a favorable effect with approximately 50% achieving steroid sparing effects and in one study, 79% (23/29) achieved full or partial control of inflammation.^{30–32} Methotrexate is also an effective agent in children with juvenile idiopathic arthritis (JIA) associated uveitis and chronic anterior or

intermediate uveitis.³³ Recently, intravitreal methotrexate has been tried with success in eyes with uveitis and uveitic CME.^{34–35} For treatment of 15 eyes with uveitic CME, statistically significant visual improvement of 4 and 4.5 lines occurred at 3 and 6 months with no statistically significant difference in vision when compared to previous treatment with corticosteroids or IVTA. Relapse occurred at a median of 4 months but reinjection had similar efficacy.³⁵

Azathioprine is widely used in organ transplantation, inflammatory bowel disease, systemic lupus erythematosus, and other autoimmune conditions. It is a pro-drug of 6-mercaptopurine, a purine nucleoside analog that interferes with DNA replication and RNA transcription which thereby inhibits actively dividing immune cells. It is absorbed orally with four-fold variation in metabolism.¹² Two enzymes, xanthine oxidase and thiopurine methyltransferase (TPMT), metabolize the drug into inactive metabolites. Allopurinol, an inhibitor of xanthine oxidase used in the treatment of gout, is contraindicated. TPMT genetic polymorphisms have been linked to azathioprine induced myelosuppression from the accumulation of toxic metabolites. Patients can be tested for this enzyme and their dose adjusted.³⁶ Doses typically used in uveitis begin at 1 mg/kg/day and can be increased to 2mg a day. The most common side effects include gastrointestinal intolerance. Rarer side effects include hepatotoxicity, occurring in 2%, and myelosuppression. Both a complete blood count and liver function tests need to be monitored during treatment.¹²

There have been a limited number of randomized clinical trials evaluating the efficacy of azathioprine in inflammatory disease. The SITE study reviewed 145 patients treated with azathioprine and showed a moderate success with 62% of active patients gaining inactivity and 47% of patients achieving corticosteroid sparing control. Greatest success was found in intermediate uveitis. Other studies include its use in Behcet's disease and in anterior uveitis.^{37–38}

Mycophenolate mofetil (MMF) is used in organ transplant rejection and multiple autoimmune diseases.³⁹ It selectively inhibits the inosine-5-monophosphate dehydrogenase in the *de novo* purine synthesis pathway and thus selectively inhibits B and T lymphocytes which depend on the *de novo* pathway since other cells can recycle nucleotides via the salvage pathway.⁴⁰ Dosing begins at 500 mg bid to a maximum of 1500 mg bid. Most common side effects are gastrointestinal and can be lessened with the salt preparation, mycophenolate sodium. Uncommon side effects include leukopenia, lymphocytopenia, and elevation of liver enzymes.⁴¹ Recently, progressive multifocal leukoencephalopathy (PML) has been described among renal transplant patients receiving MMF along with other concomitant immunosuppressives.⁴²

In ocular inflammatory disease, MMF has been shown to be effective in combination with steroids or another immunomodulatory treatment as well as monotherapy.^{43–49} As monotherapy, 65% of patients in a cohort of 54 achieved control of ocular inflammation.⁴⁵ As a steroid sparing agent, success ranged from 54% to as high as 82%.^{45, 48} The largest study to date included 236 patients with 53% achieving complete control of inflammation at 6 months and 73% at 1 year while as a steroid sparing agent 41% of patients at 6 months and 55% of patients at 1 year achieved a dosage of 10 mg or less of prednisone.⁴⁹

3.3 T-cell Inhibitors

This class of agents is commonly referred to as T cell inhibitors and includes cyclosporine, tacrolimus, and sirolimus. Cyclosporine is the most commonly used of the T-cell inhibitors and was first used in 1978 for renal transplant patients and later with extensive work by Nussenblatt et al. in an animal model of experimental autoimmune uveitis and with patients in 1983.^{50–51} Cyclosporine is an 11 amino acid peptide derived from fungus that

preferentially inhibits antigen triggered signal transduction of T-lymphocytes by forming a complex with cyclophilin which binds calcineurin that then inhibits the cytosolic translocation of nuclear factors and thus, inhibits lymphokine and anti-apoptotic protein expression.⁵² It is available in two formulations: as oil based gelatin capsules (Sandimmune, Novartis Pharmaceuticals, East Hanover, NJ) and a microemulsion (Neoral, Novartis Pharmaceuticals; Gengraf, Abbott Laboratories, Abbott Park, IL.)⁴¹ Because of the significantly better absorption of Neoral, Sandimmune is rarely used.

Cyclosporin is absorbed through the gut and metabolized by the liver through the cytochrome P450 enzyme system. The drug is dosed at 2–5 mg per kg in equally divided doses. Nephrotoxicity is the most serious side effect, however, at the lower doses used to treat ocular inflammatory disease compared to renal transplantation (10 mg per kg); it occurs less frequently. Serum creatinine and blood pressure monitoring is required. Toxicity occurs more frequently in patients greater than 55 years old with 3-fold greater discontinuation of therapy compared to patients aged 18 to 39 years old.⁵² It has been used safely in children with severe, sight-threatening uveitis with initial rises in creatinine at 6 months that later resolved.⁵³ Other adverse effects include gastrointestinal upset, metabolic abnormalities, paresthesias, tremor, gingival hyperplasia, and hirsutism.¹²

Multiple studies have shown cyclosporine effective in ocular inflammation. In the SITE study of 373 patients with noninfectious ocular inflammation used as a single immunosuppressive agent, 33.4% achieved control by 6 months and 51.9% by 1 year.⁵² Four double-masked randomized, controlled clinical trials compared cyclosporine to prednisolone, colchicine, placebo, and chlorambucil.^{54–57} It was equivalent to prednisolone in patients with sight-threatening intermediate or posterior uveitis with 46% improvement in visual acuity or vitreous haze in each group.⁵⁴ In Behcet's disease, cyclosporine was found to be more effective in treating intraocular inflammation compared to conventional treatment with corticosteroids and chlorambucil or to colchicine.^{55, 57} Other ocular inflammatory diseases it has been useful in treating include birdshot chorioretinopathy (BSCR), serpiginous choroiditis, sympathetic ophthalmia, multifocal choroiditis and panuveitis, scleritis, and ocular cicatricial pemphigoid.

Tacrolimus or FK506 is a macrolide isolated from the soil fungus *Streptomyces tsukubaensis* that was originally used in solid organ transplantation. It has a similar mechanism of action to cyclosporine and binds to an intracellular binding protein, FK-binding protein, that associates with calcineurin and thus inhibits activation of T-cells and production of cytokines.⁴¹ The drug is dosed at 0.05 mg per kg per day.¹² Other dosing regimens include starting at 2 mg daily and increasing to achieve a serum trough level of 5 to 10 ng/ml followed by tapering once disease remission is achieved.⁵⁸ The side effect profile is similar to cyclosporine. In a randomized trial comparing cyclosporine to tacrolimus, efficacy was equivalent while cyclosporine was associated with a higher frequency of adverse effects that included higher blood pressure and creatinine at three months.⁵⁹

Use of tacrolimus in ocular inflammatory disease is more limited than cyclosporine. In a retrospective review of 62 patients, there was an 85% probability of achieving <10 mg prednisone at 14 months.⁵⁸ Smaller studies comparing tacrolimus to cyclosporine have also shown favorable results. In a randomized trial of 37 patients, 68% and 67% of patients taking tacrolimus and cyclosporine achieved success. In patients that become resistant or develop nephrotoxicity to cyclosporine, tacrolimus was found to stabilize vision.⁶⁰

Sirolimus (Rapamune, Wyeth Pharmaceuticals, Maidenhead, Berks, UK) is an immunosuppressive drug used in organ transplantation with a distinct mechanism of action from cyclosporine and tacrolimus. It acts on both co-stimulatory activation and cytokine-

driven pathways.⁶¹ In cells it binds to FK binding protein-12 (FKBP-12) which forms a complex that then binds to and inhibits the activation of the mammalian target of sirolimus (mTOR) and thereby suppresses cytokine driven T cell proliferation.⁶² It is metabolized by the cytochrome P450-3A4 isoenzyme (CYP3A4) resulting in multiple metabolites.⁶¹ Dosing is not as well established for ocular inflammatory disease but generally follows the transplant maintenance doses. In the transplant literature, therapeutic drug monitoring is seen as beneficial because of the large variability in pharmacokinetics.⁶³ When dosed with cyclosporine which acts on the same metabolic pathway, the target range is lowered to 4 to 12 ug/mL. In cyclosporine sparing regimens, the target range is increased to 12 to 20 ug/mL.⁶¹ One approach followed is a loading dose of 6 mg followed by 2 mg daily doses with increases based on the trough blood levels measured every 4 weeks.⁶⁴ Side effects include hematological, hypercholesterolemia, arthralgias, extremity edema, an impaired wound healing. Lipid levels should be monitored during treatment.

There are few studies evaluating the use of sirolimus in uveitis. In a case report of a patient with punctate inner choroidopathy and associated choroidal neovascularization, Nussenblatt et al. treated the inflammatory membrane and reported a reduction in retinal thickness on OCT and leakage on FA within weeks of starting treatment that was maintained for a follow up of 9 months.⁶² In a small prospective study, five of eight patients with severe noninfectious uveitis responded with either a decrease in dose or discontinuation of steroids.⁶⁴

3.4 Alkylating Agents

The alkylating agents, cyclophosphamide and chlorambucil, comprise a class of drugs that work by alkylating DNA resulting in DNA cross-linking and inhibition of DNA synthesis.⁴¹ They were originally developed for the treatment of cancers and are now widely used for rheumatologic conditions. Because of serious, life-threatening side effects; their use is limited to severe, sight-threatening uveitis that has not responded to less toxic therapy. Close laboratory monitoring is required.⁶⁵

Cyclophosphamide, a mustard gas derivative, whose active metabolites alkylate the purines of DNA and RNA resulting in cross-linking and impaired cell division, results in decreased numbers of T and B lymphocytes. It is converted to multiple metabolites by hepatic microsomal enzymes and extensively metabolized by the kidney.¹² One of the metabolites, acrolein, is thought to be responsible for bladder toxicity.⁶⁶ Dosing for ocular inflammation is commonly 1–3 mg/kg orally with adjustments made based on the degree of leukopenia and response. Alternatively, it can be given as IV pulse therapy 1gm/m² body surface area every 3–4 weeks.⁶⁷ For mild leukopenia, the dose can be adjusted 25–50 mg with a white blood cell count no lower than 3000/mm³. Weekly complete blood count and platelet count and urinalysis should be checked until stable and then can be monitored monthly. If the white blood cell count falls below 2500/mm³, therapy should be interrupted.¹²

The most common side effect is dose dependent myelosuppression that is reversible with discontinuation of therapy as well as opportunistic infections. The most feared complication is bladder toxicity manifested by hemorrhagic cystitis and later by the development of bladder cancer. Preventative measures include adequate hydration and mesna, a thiol compound thought to be a uroprotective agent.⁶⁶ It is a teratogenic agent and, therefore, contraception must be used in patients of childbearing age. Patients also need counseling regarding their future fertility as cyclophosphamide can result in gonadal and ovarian failure with resultant sterility. Other common side effects include nausea, vomiting, and alopecia.

It is commonly used in systemic lupus erythematosus and vasculitides such as Wegener's Granulomatosis where it became the treatment of choice in this formerly fatal disease.⁶⁸

Most of the information in uveitis comes from small case reports but the recent SITE data involved 215 patients who achieved control of inflammation in 49% at 6 months and 76% within 12 months but also showed a trend for slightly increased cancer-related mortality.⁶⁹ When given as IV pulse therapy, there may be fewer side effects by avoiding prolonged exposure. In a study of 38 patients that were treated for at least 2 months, 55% of patients achieved remission and 41% were able to discontinue steroids completely.⁶⁷

Chlorambucil is another alkylating agent that works similarly to cyclophosphamide in that DNA cross-linking interferes with DNA replication and transcription when an alkyl group replaces a hydrogen ion.¹² The onset of action is slower than cyclophosphamide. Two dosing regimens are used: either 0.1–0.2 mg/kg as a single dose for 1 year after quiescence of disease in order to induce long term remission or a short term, high dose therapy of 2 mg per day for 1 week followed by 2 mg per day each week until the inflammation is suppressed, the WBC count decreases to 2400 cells per microliter, or the platelet count drops below 100,000 cells per microliter.^{70–71} Weekly monitoring of the CBC is required until blood counts stabilize. Side effects include reversible bone marrow suppression, opportunistic infections, nausea, and gonadal dysfunction including sterility and amenorrhea. It is teratogenic and contraindicated in pregnancy.¹²

Because of the risks associated with chlorambucil, its use is generally restricted to severe sight threatening uveitis such as in Behcet's or sympathetic ophthalmia.^{71–72} Longer term follow up of patients with severe sight-threatening uveitis using the short term high dose therapy reported 77% of patients achieving a remission with an average follow up of 4 years.⁷³ For patients with the longer term low dose therapy, 68% had a positive clinical response with 50% achieving remission at the end of the follow up period (mean 46 months).⁷⁴

3.5 Biologics

Biologic agents include a class of drugs that are designed based on the molecular understanding of the immune system. Tumor necrosis factor- α (TNF- α) is a well known pro-inflammatory cytokine that has been shown to play a key role in inflammatory disease. TNF- α inhibition with antibodies has been found to suppress experimental autoimmune uveitis.⁷⁵ TNF- α inhibitors include infliximab and adalimumab which are monoclonal antibodies against TNF- α and etanercept, a soluble TNF- α receptor. Certolizumab pegol and golimumab have only been recently introduced and there is limited clinical experience.⁷⁶

Infliximab (Remicade, Centocor Ortho Biotech, Malvern, PA) is a 149 kilodalton chimeric IgG1 monoclonal antibody composed of human constant and murine variable regions. It is approved for use in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis and commonly used in Crohn's disease. Dosing ranges from 3 mg/kg to 10 mg/kg from 0–8 weeks.¹² One employed strategy is 3 mg/kg for those on concomitant noncorticosteroid therapy and otherwise 5 mg/kg at 0, 2, and 6 weeks and then every 4 to 8 weeks with increases in dose based on breakthrough inflammation.⁷⁷ Adverse effects include development of an infusion reaction, opportunistic infections including latent tuberculosis, malignancies, lupus like reactions and elevations of autoantibodies, and elevated transaminases. Patients must be screened for hepatitis B and C as well as tuberculosis with chest radiography and the tuberculin skin test.⁷⁸

Much of the evidence of the effectiveness of infliximab in ocular inflammatory disease comes from studies on its use in Behcet's disease. In cyclosporine resistant patients both 5 mg/kg and 10 mg/kg were found to reduce the number of attacks of uveitis. When retrospectively compared to cyclosporine during the initial 6 months of disease, infliximab was more successful at reducing the number of attacks (1.2 uveitis episodes with

cyclosporine vs. 0.4 with infliximab, $P<0.0005$).^{79–80} Similar results were found in patients treated with infliximab versus conventional immunosuppression for Behcet's.⁸¹ For treatment of refractory uveitis, 3 of 4 patients were found to benefit from infliximab in a 2 year prospective study.⁷⁷ Infliximab has been found to be both safe and effective in children although higher doses were required.^{82–83}

Adalimumab (Humira, Abbott, Chicago, IL) is a fully humanized monoclonal antibody against TNF- α administered as a 40 mg subcutaneous injection every 1 to 2 weeks. Because adalimumab is fully humanized, there is less risk of developing autoantibodies and severe allergic reactions; otherwise, side effect profile is similar to infliximab.⁸⁴

Adalimumab has been found to be successful in treating Behcet's disease, refractory uveitis, and juvenile idiopathic arthritis (JIA) associated uveitis.^{85–87} A case report of three patient's with Behcet's disease in remission were transitioned from infliximab to adalimumab for a follow up period of 11–24 months with no recurrences.⁸⁵ Adalimumab was demonstrated effective in retrospective studies on children treated for chronic anterior uveitis or JIA associated uveitis with no recurrences or more than 2 relapses less than before treatment in 88% in one study and 35% improvement (defined as inactive disease or 2 step decrease in inflammation) in another study.^{87–88}

Etanercept (Enbrel, Immunex Corp., Seattle, WA) is also given subcutaneously as a 25 mg weekly injection. It has been found to be less effective than infliximab and adalimumab in the treatment of uveitis, however, it is quite effective in systemic disease such as rheumatoid arthritis. In a retrospective review comparing patients treated with infliximab and etanercept, both the number of recurrences and ocular inflammation was improved with infliximab compared to etanercept (59% decrease in recurrences vs. 0%).⁸⁹ In JIA associated uveitis, patients taking etanercept had more uveitis flares per year and worse inflammatory activity compared to patients taking infliximab.⁹⁰

Cytokine receptor antibodies include drugs such as daclizumab, a humanized monoclonal antibody directed against the alpha subunit of the interleukin 2 receptor (CD25) present on activated T-cells. The FDA originally approved the drug in 1997 for renal allograft rejection and it is now widely used in autoimmune diseases such as multiple sclerosis, other solid organ transplants, and human T cell leukemia virus-1 associated T-cell leukemia. The drug is administered as 1 to 2 mg/kg infusions every 2 to 4 weeks. Side effects include rashes, edema, granulomatous reactions, viral respiratory infections, elevated liver enzymes, and leukopenia.^{12, 91–92}

Multiple studies have shown daclizumab effective in anterior, intermediate, posterior or panuveitis as well as JIA associated uveitis.^{92–95} There is a subcutaneous form of daclizumab that has had favorable results.⁹⁶ In BSCR it stabilized and or improved vision and ocular inflammation in 6 of 8 patients.⁹¹ In Behcet's disease, daclizumab was not found to be more effective than conventional immunosuppression; however, there was a low attack rate overall which may have skewed results.⁹⁷ Despite the success of daclizumab in treating ocular inflammatory disorders, it was recently pulled from the market because of diminishing market demand and availability of alternative agents and not due to safety issues (based on a September 2009 Hoffmann-La Roche Inc. drug announcement.).

Interferon alpha-2a (INF- α 2a) was first introduced in 1981 and found to be successful in the treatment of uveitis associated with Behcet's disease. It is a cytokine released by somatic cells in viral infections which exerts antiviral, antiproliferative, antiangiogenic, and immunomodulatory effects.⁹⁸ Dosing ranges from 3–9 million units per day given once daily to three times weekly. Side effects include a transient flu like syndrome, fatigue,

depression, neutropenia, elevation of liver enzymes, and rarely INF- α 2a retinopathy. Paracetamol can be given to temporize flu like symptoms⁸⁴

In Behcet's diseases, both open studies and case reports have demonstrated the effectiveness of INF- α 2a in treating severe ocular Behcet's disease. In a review summarizing previous reports, 94% of patient's with Behcet's had a partial or complete response.⁹⁹ It does not seem to be as effective as in other forms of uveitis compared to uveitis associated with Behcet's disease (59% vs. 83%; $p=0.07$).¹⁰⁰ INF- α 2a is also capable of inducing remission in Behcet's. In a study of 53 patients, 98.1% responded and 50% remained in remission after 46 months of follow up.¹⁰¹

INF- α 2a is also effective at treating chronic, refractory CME in noninfectious uveitis. It was studied in 24 patients given subcutaneously based on weight as 3 or 6 million units per day and tapered over 6 months in a stepwise manner. Complete resolution of CME occurred in 62.5%, partial resolution in 25%, and ineffective in 12.5%.¹⁰² If patients are able to tolerate the side effect profile (flu like symptoms, fatigue and depression), INF- α 2a may be an additional tool besides corticosteroids in treating uveitic CME.

Interferon alpha-2b (INF- α 2B) is an alternative agent effective in treating Behcet's. In a meta-analysis of 32 papers published, comparison of INF- α 2a and INF- α 2b found that remissions were more common with INF- α 2a than with INF- α 2b and this was especially the case with ocular manifestations (91% vs. 6%) and less for mucocutaneous lesions (51% vs. 6%). However, the authors caution that when complete and partial remissions are included, these differences are less obvious.⁹⁹

Rituximab (Rituxan, Genentech, San Francisco, CA) is a chimeric monoclonal antibody against CD20, a B cell marker, which results in depletion of B cells. It was originally developed for the treatment of B cell lymphomas but has been found to be effective in autoimmune diseases traditionally thought to be T cell mediated diseases.¹⁰³ Based on guidelines for rheumatoid arthritis, dosing is 1000 mg given at day 0 and day 14. Patients need to be screened for hepatitis B and C and given lamivudine prophylaxis for positive results.¹⁰⁴ Side effects include hypersensitivity or infusion related reactions, infections, and PML.^{103, 105}

There are a limited number of case reports showing rituximab effective in ocular inflammatory disease.^{106–110} It has been used successfully in scleritis associated with rheumatoid arthritis and Wegener's granulomatosis with complete resolution after two 1000 mg infusions with a 9 and 12 month follow up.^{109–110} In a consecutive case series of 10 patients with refractory ophthalmic Wegener's, all 10 patients achieved remission within 7 months and a decrease in the antineutrophilic cytoplasmic antibodies.¹⁰⁶ For retinal vasculitis associated with Behcet's disease, there was success in a patient who failed treatment with etanercept, azathioprine, and prednisolone after receiving two 1000 mg infusions and remained recurrence free for 24 months of follow up.¹⁰⁷

Bevacizumab (Avastin[™], Genentech, South San Francisco, CA) and ranibizumab (Lucentis[™]; Genentech Inc, South San Francisco, CA) are both monoclonal antibodies to vascular endothelial growth factor (VEGF). Ranibizumab was designed specifically for ocular use and received FDA approval for the treatment of choroidal neovascularization in age related macular degeneration while bevacizumab is FDA approved for colorectal cancer but currently used off label intraocularly for ocular disease. Previous work has shown increased levels of VEGF in the aqueous humor of eyes with uveitis and CME compared to eyes with uveitis and without CME, thus paving the way for use in uveitic macular edema.¹¹¹ In a retrospective, interventional case series of patients with CME refractory to conventional therapy, bevacizumab was found effective at improving vision and macular

edema.¹¹² In a prospective, case series of 6 patients with quiet uveitis and CME refractory to standard therapy, ranibizumab was given monthly for three months followed by reinjection as needed. Both vision and central retinal thickness improved at 3 and 6 months with no adverse effects noted.¹¹³

4. Current Research Goals

The number of therapeutic options in uveitis has expanded vastly over the last 30 years. However, none of these agents represent the perfect single drug with each having particular drawbacks. Current strategies to develop new drugs include reformulation of current drugs in an effort to improve their efficacy and reduce their side effect profile. In particular, voclosporin, similar to cyclosporin, represents one such agent. Other strategies employ formulating new drugs, particularly biologics, targeting specific receptors, cytokines or signalling pathways. As our understanding of autoimmune diseases expands, new targets and approaches are becoming available.

5. Competitive Environment

Emerging drugs for the treatment of uveitis include drugs in existing drug classes that have undergone reformulation and drugs targeting a novel mechanism of action (see Table 2). AIN457 is a monoclonal antibody which inhibits interleukin-17 (IL-17). IL-17 is secreted by Th-17 cells and has evolved as a key mediator in the pathogenesis of autoimmune disease. It is under development by Novartis for the treatment of uveitis, psoriasis, and other inflammatory conditions and currently in phase III clinical trials.

Apremilast is a selective cytokine inhibitory drug under development by Celgene which inhibits phosphodiesterase IV and thereby inhibits TNF- α production and suppresses the immune response. It would provide an oral medication and thus avoid the cost and hassle of injections of current anti-TNF α inhibitors.¹¹⁴ It is currently in phase II clinical trials and is being studied in psoriasis, Behcet's disease, and rheumatoid arthritis. There are no current uveitis trials.

ESBA-105 is a topical anti-TNF α single chain antibody under development by Alcon for the treatment of ocular conditions including uveitis, diabetic retinopathy, and age related macular degeneration. Previous work has shown good anterior and posterior intraocular penetration.¹¹⁵ If effective, it would avoid the risk of systemic exposure by other anti-TNF α inhibitors.

Voclosporin (Luveniq) is a calcineurin inhibitor under development by Lux Biosciences for the treatment of uveitis. In earlier studies it was shown to be more potent and less toxic than cyclosporine in vivo and in vitro studies.^{116–118} Three prospective, randomized, multi-center, double-masked, parallel-group, dose-ranging, placebo-controlled studies were reported in 2009. In the first study evaluating active posterior disease, voclosporin led to more than one step improvement in vitreous haze compared to placebo, in the second study evaluating patients with quiescent disease, there was a statistically significant reduction in eye inflammation with voclosporin compared with placebo ($P=0.045$), but it did not meet the primary endpoint of all-cause therapeutic failure. In the third study evaluating anterior inflammation, voclosporin failed to distinguish itself from placebo (Rosenbaum JT, et al. 2009 ARVO E-Abstract 2009 2021). Clearly, additional studies are needed to establish voclosporin's efficacy.

MM-093 is a recombinant human alpha-fetoprotein under development by Merrimack for multiple autoimmune disorders including a recently completed phase II pilot study on 20 patients with sarcoid or birdshot uveitis.

EGP-437 is a formulation of dexamethasone phosphate under development by EyeGate Pharma for the treatment of uveitis and dry eye. They are currently in phase II and III trials.

Basiliximab (Simulect, Novartis, Basel, Switzerland) is a chimeric monoclonal antibody against CD25 for renal allograft rejection. It may be an alternative agent to daclizumab now that it has been withdrawn from the market. Other potential uses include systemic sclerosis and inflammatory bowel disease.^{119–120}

Everolimus (Zortress, Novartis, Basel, Switzerland) is an orally-active sirolimus analog which acts as an mTOR inhibitor. It is currently FDA approved for the treatment of renal cell cancer but like sirolimus may have potential applications in ocular inflammatory disease.

Canakinumab, (Ilaris[™], Novartis, New York, NY) is a fully humanized anti interleukin-1 β monoclonal antibody that selectively blocks interleukin-1. It was approved in the US and EU in 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS) which includes rare genetic disorders such as Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease (NOMID), and familial cold autoinflammatory syndrome.¹²¹ It may have potential use in ocular inflammatory disease as these syndromes can present with ocular inflammation.

6. Potential Development Issues

Drug development in the current era has never been more exciting or more expensive. New targets are emerging from the vast amount of molecular research, however, at the same time; the cost to bring a drug to market has never been more daunting. The estimates of new drug development costs vary from 800 to almost 1 billion dollars to bring a drug to the point of FDA marketing.¹²² Many of the new biologic agents are expensive to administer and require clinical monitoring. The cost of infliximab is estimated at \$13,000–\$20,000 per patient per year.⁷⁶ In uveitis in particular, there is a need for more randomized controlled trials to evaluate the safety and efficacy of agents. Furthermore, many of the side effects of the agents so successful in treating rheumatologic conditions are difficult to justify when PML is included in the risk and benefit discussion. Local delivery systems that provide these potent drugs are needed when the disease is limited to the eye.

7. Expert Opinion

Among the studies quoted in this paper in support or against a particular drug, most are retrospective reviews, smaller studies, and have no standard definition of success. The SITE studies provide the largest multicenter cohort of patients to date evaluating the effectiveness of the antimetabolites and cyclophosphamide both in terms of control of ocular inflammation and steroid sparing success in a standardized fashion. Methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide all achieved at least 50% success at controlling ocular inflammation within 1 year. This same data is not yet available for biologic agents although there are smaller studies showing their efficacy. The ultimate goal in uveitis is to induce a drug free remission. Sadly, few drugs can reach this level of success and obtaining disease control with the minimum amount of treatment is the most realistic and achievable goal at this time. Infliximab has shown some success in treating Behcet's and chlorambucil was shown in smaller studies to induce remission. (Use of chlorambucil is limited by its toxicity and potential for severe side effects.) Success at this time is defined by treatments able to maintain relative quiescence, occasional drug free holidays, and tapering to physiologic doses of steroids.

Other concerns with the newer biologic agents and current immunosuppressive therapy are whether their associated risks are warranted. This is significant in light of the recent reports resulting in a black box warning for mycophenolate mofetile for PML and the data from the SITE study suggesting an increased risk of mortality (overall and cancer) with anti-TNF inhibitors.^{42, 123} The patient needs to be well aware of the risks and benefits of systemic treatment for ocular disease and whether they are willing to assume potentially life long risks versus the burden of further vision loss. The question is more difficult in pediatric patients in which we do not have long-term follow up data

The continued advancement of the field of uveitis hinges on better understanding of immunology and uveitic diseases in order to provide more targeted treatment. Much of what is known in immunology derives from the mouse model, but the question arises whether this can be applied to the human. Although we understand the mechanism of some current drugs, there are others that we do not. Even though interferon- α 2a has been available since 1981, why it is successful in Behcet's disease is still unknown. Among the anti-TNF α agents, etanercept can treat rheumatoid arthritis but is poor at treating uveitis and Crohn's disease. In the next 5–10 years, a greater push for uveitis studies both in understanding the diverse diseases that comprise it and a push for drugs that treat intraocular inflammation must be made. We must advocate for early diagnosis and aggressive treatment to prevent needless vision loss in our patients. Great strides have been made in uveitis treating once blinding diseases; now we must continue that journey for safe and proven treatments.

Acknowledgments

This research is supported by the NEI Intramural Research Program

References

1. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep; 140(3):509–16. [PubMed: 16196117]
2. Chang JH, Wakefield D. Uveitis: a global perspective. Ocul Immunol Inflamm. 2002 Dec; 10(4): 263–79. [PubMed: 12854035]
3. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 2005 Jul-Aug; 50(4):364–88. [PubMed: 15967191]
4. Power WJ, Rodriguez A, Pedroza-Seres M, Foster CS. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998 Sep; 105(9):1646–51. [PubMed: 9754172]
5. Nussenblatt RB. The natural history of uveitis. Int Ophthalmol. 1990 Oct; 14(5–6):303–8. [PubMed: 2249907]
6. Darrell RW, Wagener HP, Kurland LT. Epidemiology of uveitis. Incidence and prevalence in a small urban community. Arch Ophthalmol. 1962 Oct; 68:502–14. [PubMed: 13883604]
7. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. Ophthalmology. 2004 Mar; 111(3):491–500. discussion 00. [PubMed: 15019324]
8. Rothova A, Suttrop-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996 Apr; 80(4):332–6. [PubMed: 8703885]
9. Durrani OM, Meads CA, Murray PI. Uveitis: a potentially blinding disease. Ophthalmologica. 2004 Jul-Aug; 218(4):223–36. [PubMed: 15258410]
10. Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past, the present, and the future. Surv Ophthalmol. 2008 Mar-Apr; 53(2):139–49. [PubMed: 18348879]
11. Dana MR, Merayo-Llodes J, Schaumberg DA, Foster CS. Prognosticators for visual outcome in sarcoid uveitis. Ophthalmology. 1996 Nov; 103(11):1846–53. [PubMed: 8942880]

12. Jabs DA, Rosenbaum JT. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2001 May;131(5):679. [PubMed: 11354352]
13. Reed JB, Morse LS, Schwab IR. High-dose intravenous pulse methylprednisolone hemisuccinate in acute Behcet retinitis. *Am J Ophthalmol*. 1998 Mar; 125(3):409–11. [PubMed: 9512170]
14. Becker B, Mills DW. Elevated Intraocular Pressure Following Corticosteroid Eye Drops. *JAMA*. 1963 Sep 14;185:884–6. [PubMed: 14043096]
15. Urban RC Jr, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol*. 1986 Sep-Oct; 31(2): 102–10. [PubMed: 3541262]
16. Helm CJ, Holland GN. The effects of posterior subtenon injection of triamcinolone acetonide in patients with intermediate uveitis. *Am J Ophthalmol*. 1995 Jul; 120(1):55–64. [PubMed: 7611330]
17. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A. Intravitreal and orbital floor triamcinolone acetonide injections in noninfectious uveitis: a comparative study. *Ophthalmic Res*. 2009; 42(2):81–6. [PubMed: 19478546]
18. Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis. *Ophthalmology*. 2005 Nov; 112(11):1916, e1–7. [PubMed: 16171868]
19. Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. *Br J Ophthalmol*. 2003 Jan; 87(1):24–7. [PubMed: 12488256]
20. Moshfeghi DM, Kaiser PK, Bakri SJ, Kaiser RS, Maturi RK, Sears JE, et al. Presumed sterile endophthalmitis following intravitreal triamcinolone acetonide injection. *Ophthalmic Surg Lasers Imaging*. 2005 Jan-Feb; 36(1):24–9. [PubMed: 15688968]
21. Moshfeghi DM, Kaiser PK, Scott IU, Sears JE, Benz M, Sinesterra JP, et al. Acute endophthalmitis following intravitreal triamcinolone acetonide injection. *Am J Ophthalmol*. 2003 Nov; 136(5): 791–6. [PubMed: 14597028]
22. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. *Arch Ophthalmol*. 2008 Sep; 126(9):1191–201. [PubMed: 18779477]
23. Galor A, Margolis R, Kaiser PK, Lowder CY. Vitreous band formation and the sustained-release, intravitreal fluocinolone (Retisert) implant. *Arch Ophthalmol*. 2007 Jun; 125(6):836–8. [PubMed: 17562999]
24. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. *Am J Ophthalmol*. 2010 Apr; 149(4): 550–61. e10. [PubMed: 20097325]
25. Taylor SR, Isa H, Joshi L, Lightman S. New developments in corticosteroid therapy for uveitis. *Ophthalmologica*. 2010; 224(Suppl 1):46–53. [PubMed: 20714181]
26. Kim EC, Foster CS. Immunomodulatory therapy for the treatment of ocular inflammatory disease: evidence-based medicine recommendations for use. *Int Ophthalmol Clin*. 2006 Spring;46(2):141–64. [PubMed: 16770160]
27. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *N Engl J Med*. 1948 Jun 3; 238(23):787–93. [PubMed: 18860765]
28. Wong VG, Hersh EM. Methotrexate in the therapy of cyclitis. *Trans Am Acad Ophthalmol Otolaryngol*. 1965; 69:279 – 93.
29. Gangaputra S, Newcomb CW, Liesegang TL, Kacmaz RO, Jabs DA, Levy-Clarke GA, et al. Methotrexate for ocular inflammatory diseases. *Ophthalmology*. 2009 Nov; 116(11):2188–98. e1. [PubMed: 19748676]
30. Samson CM, Waheed N, Baltatzis S, Foster CS. Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. *Ophthalmology*. 2001 Jun; 108(6):1134–9. [PubMed: 11382642]
31. Bom S, Zamiri P, Lightman S. Use of methotrexate in the management of sight-threatening uveitis. *Ocul Immunol Inflamm*. 2001 Mar; 9(1):35–40. [PubMed: 11262666]
32. Kaplan-Messas A, Barkana Y, Avni I, Neumann R. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. *Ocul Immunol Inflamm*. 2003 Jun; 11(2):131–9. [PubMed: 14533032]

33. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol*. 2005 Jul; 89(7):806–8. [PubMed: 15965154]
34. Hardwig PW, Pulido JS, Erie JC, Baratz KH, Buettner H. Intraocular methotrexate in ocular diseases other than primary central nervous system lymphoma. *Am J Ophthalmol*. 2006 Nov; 142(5):883–5. [PubMed: 17056381]
35. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. *Ophthalmology*. 2009 Apr; 116(4):797–801. [PubMed: 19344827]
36. Clunie GP, Lennard L. Relevance of thiopurine methyltransferase status in rheumatology patients receiving azathioprine. *Rheumatology (Oxford)*. 2004 Jan; 43(1):13–8. [PubMed: 14566029]
37. Yazici H, Pazarli H, Barnes CG, Tuzun Y, Ozyazgan Y, Silman A, et al. A controlled trial of azathioprine in Behcet's syndrome. *N Engl J Med*. 1990 Feb 1; 322(5):281–5. [PubMed: 2404204]
38. Mathews JD, Crawford BA, Bignell JA, Mackay IR. Azathioprine in active chronic iridocyclitis. A double-blind controlled trial. *Br J Ophthalmol*. 1969; 53:327–33. [PubMed: 4890826]
39. Lipsky JJ. Mycophenolate mofetil. *Lancet*. 1996 Nov 16; 348(9038):1357–9. [PubMed: 8918281]
40. Miehsler W, Reinisch W, Moser G, Gangl A, Vogelsang H. Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol*. 2001 Mar; 96(3):782–7. [PubMed: 11280551]
41. Okada AA. Immunomodulatory therapy for ocular inflammatory disease: a basic manual and review of the literature. *Ocul Immunol Inflamm*. 2005 Sep-Oct; 13(5):335–51. [PubMed: 16419419]
42. Neff RT, Hurst FP, Falta EM, Bohlen EM, Lentine KL, Dharnidharka VR, et al. Progressive multifocal leukoencephalopathy and use of mycophenolate mofetil after kidney transplantation. *Transplantation*. 2008 Nov 27; 86(10):1474–8. [PubMed: 19034021]
43. Kilmartin DJ, Forrester JV, Dick AD. Rescue therapy with mycophenolate mofetil in refractory uveitis. *Lancet*. 1998 Jul 4; 352(9121):35–6. [PubMed: 9800750]
44. Larkin G, Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. *Ophthalmology*. 1999 Feb; 106(2):370–4. [PubMed: 9951492]
45. Baltatzis S, Tufail F, Yu EN, Vredevelde CM, Foster CS. Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology*. 2003 May; 110(5):1061–5. [PubMed: 12750115]
46. Deuter CM, Doycheva D, Stuebiger N, Zierhut M. Mycophenolate sodium for immunosuppressive treatment in uveitis. *Ocul Immunol Inflamm*. 2009 Nov-Dec; 17(6):415–9. [PubMed: 20001262]
47. Lau CH, Comer M, Lightman S. Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation. *Clin Experiment Ophthalmol*. 2003 Dec; 31(6):487–91. [PubMed: 14641155]
48. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology*. 2005 Aug; 112(8):1472–7. [PubMed: 16061096]
49. Daniel E, Thorne JE, Newcomb CW, Pujari SS, Kacmaz RO, Levy-Clarke GA, et al. Mycophenolate mofetil for ocular inflammation. *Am J Ophthalmol*. 2010 Mar; 149(3):423–32. e1–2. [PubMed: 20042178]
50. Nussenblatt RB, Rodrigues MM, Wacker WB, Cevario SJ, Salinas-Carmona MC, Gery I. Cyclosporin a. Inhibition of experimental autoimmune uveitis in Lewis rats. *J Clin Invest*. 1981 Apr; 67(4):1228–31. [PubMed: 7204576]
51. Nussenblatt RB, Palestine AG, Rook AH, Scher I, Wacker WB, Gery I. Treatment of intraocular inflammatory disease with cyclosporin A. *Lancet*. 1983 Jul 30; 2(8344):235–8. [PubMed: 6135075]
52. Kacmaz RO, Kempen JH, Newcomb C, Daniel E, Gangaputra S, Nussenblatt RB, et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology*. 2010 Mar; 117(3):576–84. [PubMed: 20031223]
53. Walton RC, Nussenblatt RB, Whitcup SM. Cyclosporine therapy for severe sight-threatening uveitis in children and adolescents. *Ophthalmology*. 1998 Nov; 105(11):2028–34. [PubMed: 9818601]

54. Nussenblatt RB, Palestine AG, Chan CC, Stevens G Jr, Mellow SD, Green SB. Randomized, double-masked study of cyclosporine compared to prednisolone in the treatment of endogenous uveitis. *Am J Ophthalmol*. 1991 Aug 15; 112(2):138–46. [PubMed: 1867297]
55. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behcet's disease. *Lancet*. 1989 May 20; 1(8647):1093–6. [PubMed: 2566048]
56. de Vries J, Baarsma GS, Zaal MJ, Boen-Tan TN, Rothova A, Buitenhuis HJ, et al. Cyclosporin in the treatment of severe chronic idiopathic uveitis. *Br J Ophthalmol*. 1990 Jun; 74(6):344–9. [PubMed: 2198928]
57. BenEzra D, Cohen E, Chajek T, Friedman G, Pizanti S, de Courten C, et al. Evaluation of conventional therapy versus cyclosporine A in Behcet's syndrome. *Transplant Proc*. 1988 Jun; 20(3 Suppl 4):136–43. [PubMed: 3381269]
58. Hogan AC, McAvoy CE, Dick AD, Lee RW. Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. *Ophthalmology*. 2007 May; 114(5):1000–6. [PubMed: 17467532]
59. Murphy CC, Greiner K, Plskova J, Duncan L, Frost NA, Forrester JV, et al. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. *Arch Ophthalmol*. 2005 May; 123(5):634–41. [PubMed: 15883282]
60. Kilmartin DJ, Forrester JV, Dick AD. Tacrolimus (FK506) in failed cyclosporin A therapy in endogenous posterior uveitis. *Ocul Immunol Inflamm*. 1998 Jun; 6(2):101–9. [PubMed: 9689640]
61. Buhaescu I, Izzedine H, Covic A. Sirolimus--challenging current perspectives. *Ther Drug Monit*. 2006 Oct; 28(5):577–84. [PubMed: 17038868]
62. Nussenblatt RB, Coleman H, Jirawuthiworavong G, Davuluri G, Potapova N, Dahr SS, et al. The treatment of multifocal choroiditis associated choroidal neovascularization with sirolimus (rapamycin). *Acta Ophthalmol Scand*. 2007 Mar; 85(2):230–1. [PubMed: 17305748]
63. Aspeslet LJ, Yatscoff RW. Requirements for therapeutic drug monitoring of sirolimus, an immunosuppressive agent used in renal transplantation. *Clin Ther*. 2000; 22(Suppl B):B86–92. [PubMed: 10823376]
64. Shanmuganathan VA, Casely EM, Raj D, Powell RJ, Joseph A, Amoaku WM, et al. The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol*. 2005 Jun; 89(6):666–9. [PubMed: 15923497]
65. Kurup SK, Chan CC. Immunotherapeutic approaches in ocular inflammatory diseases. *Arch Immunol Ther Exp (Warsz)*. 2005 Nov-Dec; 53(6):484–96. [PubMed: 16407781]
66. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum*. 2010 Jan; 62(1):9–21. [PubMed: 20039416]
67. Durrani K, Papaliodis GN, Foster CS. Pulse IV cyclophosphamide in ocular inflammatory disease: efficacy and short-term safety. *Ophthalmology*. 2004 May; 111(5):960–5. [PubMed: 15121375]
68. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med*. 1983 Jan; 98(1):76–85. [PubMed: 6336643]
69. Pujari SS, Kempen JH, Newcomb CW, Gangaputra S, Daniel E, Suhler EB, et al. Cyclophosphamide for ocular inflammatory diseases. *Ophthalmology*. 2010 Feb; 117(2):356–65. [PubMed: 19969366]
70. Mamo JG. Treatment of Behcet disease with chlorambucil. A follow-up report. *Arch Ophthalmol*. 1976 Apr; 94(4):580–3. [PubMed: 1267637]
71. Tessler HH, Jennings T. High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behcet's disease. *Br J Ophthalmol*. 1990 Jun; 74(6):353–7. [PubMed: 2378842]
72. O'Duffy JD, Robertson DM, Goldstein NP. Chlorambucil in the treatment of uveitis and meningoencephalitis of Behcet's disease. *Am J Med*. 1984 Jan; 76(1):75–84. [PubMed: 6691363]
73. Goldstein DA, Fontanilla FA, Kaul S, Sahin O, Tessler HH. Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. *Ophthalmology*. 2002 Feb; 109(2):370–7. [PubMed: 11825825]

74. Miserocchi E, Baltatzis S, Ekong A, Roque M, Foster CS. Efficacy and safety of chlorambucil in intractable noninfectious uveitis: the Massachusetts Eye and Ear Infirmary experience. *Ophthalmology*. 2002 Jan; 109(1):137–42. [PubMed: 11772593]
75. Sartani G, Silver PB, Rizzo LV, Chan CC, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. *Invest Ophthalmol Vis Sci*. 1996 Oct; 37(11):2211–8. [PubMed: 8843907]
76. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Curr Dir Autoimmun*. 2010; 11:180–210. [PubMed: 20173395]
77. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. *Arch Ophthalmol*. 2009 Jun; 127(6):819–22. [PubMed: 19506209]
78. Furst DE, Keystone EC, Fleischmann R, Mease P, Breedveld FC, Smolen JS, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. *Ann Rheum Dis*. 2010 Jan; 69(Suppl 1):i2–29. [PubMed: 19995740]
79. Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behcet's disease with refractory uveoretinitis. *J Rheumatol*. 2004 Jul; 31(7):1362–8. [PubMed: 15229958]
80. Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M. Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behcet disease. *Br J Ophthalmol*. 2010 Mar; 94(3):284–8. [PubMed: 19692382]
81. Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behcet disease. *Am J Ophthalmol*. 2008 Dec; 146(6):845–50. e1. [PubMed: 18929351]
82. Ardoin SP, Kredich D, Rabinovich E, Schanberg LE, Jaffe GJ. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol*. 2007 Dec; 144(6):844–49. [PubMed: 17953940]
83. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology*. 2006 May; 113(5):860–4. e2. [PubMed: 16545455]
84. Jap A, Chee SP. Immunosuppressive therapy for ocular diseases. *Curr Opin Ophthalmol*. 2008 Nov; 19(6):535–40. [PubMed: 18854699]
85. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behcet's disease. *Eye (Lond)*. 2007 Jun; 21(6):824–5. [PubMed: 16601736]
86. Callejas-Rubio JL, Sanchez-Cano D, Serrano JL, Ortego-Centeno N. Adalimumab therapy for refractory uveitis: a pilot study. *J Ocul Pharmacol Ther*. 2008 Dec; 24(6):613–4. author reply 14. [PubMed: 19049264]
87. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology (Oxford)*. 2008 Mar; 47(3):339–44. [PubMed: 18238789]
88. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol*. 2007 Mar; 91(3):319–24. [PubMed: 17035274]
89. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology*. 2006 Dec; 113(12):2317–23. [PubMed: 16996615]
90. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis*. 2007 Apr; 66(4):548–50. [PubMed: 17068061]
91. Sobrin L, Huang JJ, Christen W, Kafkala C, Choopong P, Foster CS. Daclizumab for treatment of birdshot chorioretinopathy. *Arch Ophthalmol*. 2008 Feb; 126(2):186–91. [PubMed: 18268208]
92. Nussenblatt RB, Fortin E, Schiffman R, Rizzo L, Smith J, Van Veldhuisen P, et al. Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase I/II clinical trial. *Proc Natl Acad Sci U S A*. 1999 Jun 22; 96(13):7462–6. [PubMed: 10377437]

93. Yeh S, Wroblewski K, Buggage R, Li Z, Kurup SK, Sen HN, et al. High-dose humanized anti-IL-2 receptor alpha antibody (daclizumab) for the treatment of active, non-infectious uveitis. *J Autoimmun.* 2008 Sep; 31(2):91–7. [PubMed: 18571896]
94. Sen HN, Levy-Clarke G, Faia LJ, Li Z, Yeh S, Barron KS, et al. High-dose daclizumab for the treatment of juvenile idiopathic arthritis-associated active anterior uveitis. *Am J Ophthalmol.* 2009 Nov; 148(5):696–703. e1. [PubMed: 19664754]
95. Nussenblatt RB, Thompson DJ, Li Z, Chan CC, Peterson JS, Robinson RR, et al. Humanized anti-interleukin-2 (IL-2) receptor alpha therapy: long-term results in uveitis patients and preliminary safety and activity data for establishing parameters for subcutaneous administration. *J Autoimmun.* 2003 Nov; 21(3):283–93. [PubMed: 14599854]
96. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, et al. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. *Ophthalmology.* 2005 May; 112(5):764–70. [PubMed: 15878055]
97. Buggage RR, Levy-Clarke G, Sen HN, Ursea R, Srivastava SK, Suhler EB, et al. A double-masked, randomized study to investigate the safety and efficacy of daclizumab to treat the ocular complications related to Behcet's disease. *Ocul Immunol Inflamm.* 2007 Mar-Apr; 15(2):63–70. [PubMed: 17558830]
98. Deuter CM, Kotter I, Wallace GR, Murray PI, Stubiger N, Zierhut M. Behcet's disease: ocular effects and treatment. *Prog Retin Eye Res.* 2008 Jan; 27(1):111–36. [PubMed: 18035584]
99. Kotter I, Gunaydin I, Zierhut M, Stubiger N. The use of interferon alpha in Behcet disease: review of the literature. *Semin Arthritis Rheum.* 2004 Apr; 33(5):320–35. [PubMed: 15079763]
100. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong du LT, et al. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. *Br J Ophthalmol.* 2007 Mar; 91(3):335–9. [PubMed: 17050581]
101. Deuter CM, Zierhut M, Mohle A, Vonthein R, Stubiger N, Kotter I. Long-term remissions after cessation of interferon alpha treatment in patients with severe uveitis due to Behcet's disease. *Arthritis Rheum.* 2010 Jun 1.
102. Deuter CM, Kotter I, Gunaydin I, Stubiger N, Doycheva DG, Zierhut M. Efficacy and tolerability of interferon alpha treatment in patients with chronic cystoid macular oedema due to non-infectious uveitis. *Br J Ophthalmol.* 2009 Jul; 93(7):906–13. [PubMed: 19321469]
103. Lim L, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. *Clin Experiment Ophthalmol.* 2006 May-Jun; 34(4):365–74. [PubMed: 16764659]
104. Perosa F, Favoino E, Vicenti C, Guarnera A, Racanelli V, De Pinto V, et al. Two structurally different rituximab-specific CD20 mimotope peptides reveal that rituximab recognizes two different CD20-associated epitopes. *J Immunol.* 2009 Jan 1; 182(1):416–23. [PubMed: 19109173]
105. Hellmich B. Update on the management of systemic vasculitis: what did we learn in 2009? *Clin Exp Rheumatol.* 2010 Jan-Feb; 28(1 Suppl 57):98–103. [PubMed: 20412713]
106. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum.* 2009 May; 60(5):1540–7. [PubMed: 19404964]
107. Sadreddini S, Noshad H, Molaeeafard M, Noshad R. Treatment of retinal vasculitis in Behcet's disease with rituximab. *Mod Rheumatol.* 2008; 18(3):306–8. [PubMed: 18438602]
108. Tappeiner C, Heinz C, Specker C, Heiligenhaus A. Rituximab as a treatment option for refractory endogenous anterior uveitis. *Ophthalmic Res.* 2007; 39(3):184–6. [PubMed: 17534119]
109. Onal S, Kazokoglu H, Koc A, Yavuz S. Rituximab for remission induction in a patient with relapsing necrotizing scleritis associated with limited Wegener's granulomatosis. *Ocul Immunol Inflamm.* 2008 Sep-Oct; 16(5):230–2. [PubMed: 19065418]
110. Iaccheri B, Androudi S, Bocci EB, Gerli R, Cagini C, Fiore T. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. *Ocul Immunol Inflamm.* 2010 Jun; 18(3):223–5. [PubMed: 20482403]

111. Fine HF, Baffi J, Reed GF, Csaky KG, Nussenblatt RB. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. *Am J Ophthalmol*. 2001 Nov; 132(5):794–6. [PubMed: 11704050]
112. Cervantes-Castaneda RA, Giuliari GP, Gallagher MJ, Yilmaz T, MacDonell RE, Quinones K, et al. Intravitreal bevacizumab in refractory uveitic macular edema: one-year follow-up. *Eur J Ophthalmol*. 2009 Jul-Aug; 19(4):622–9. [PubMed: 19551679]
113. Acharya NR, Hong KC, Lee SM. Ranibizumab for refractory uveitis-related macular edema. *Am J Ophthalmol*. 2009 Aug; 148(2):303–09. e2. [PubMed: 19427988]
114. McCann FE, Palfreeman AC, Andrews M, Perocheau DP, Inglis JJ, Schafer P, et al. Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis. *Arthritis Res Ther*. 2010 Jun 2. 12(3):R107. [PubMed: 20525198]
115. Ottiger M, Thiel MA, Feige U, Lichtlen P, Urech DM. Efficient intraocular penetration of topical anti-TNF-alpha single-chain antibody (ESBA105) to anterior and posterior segment without penetration enhancer. *Invest Ophthalmol Vis Sci*. 2009 Feb; 50(2):779–86. [PubMed: 18757511]
116. Aspeslet L, Freitag D, Trepanier D, Abel M, Naicker S, Kneteman N, et al. ISA(TX)247: a novel calcineurin inhibitor. *Transplant Proc*. 2001 Feb-Mar; 33(1–2):1048–51. [PubMed: 11267185]
117. Stalder M, Birsan T, Hubble RW, Paniagua RT, Morris RE. In vivo evaluation of the novel calcineurin inhibitor ISATX247 in non-human primates. *J Heart Lung Transplant*. 2003 Dec; 22(12):1343–52. [PubMed: 14672749]
118. Birsan T, Dambrin C, Freitag DG, Yatscoff RW, Morris RE. The novel calcineurin inhibitor ISA247: a more potent immunosuppressant than cyclosporine in vitro. *Transpl Int*. 2005 May; 17(12):767–71. [PubMed: 15827754]
119. Ong VH, Denton CP. Innovative therapies for systemic sclerosis. *Curr Opin Rheumatol*. 2010 May; 22(3):264–72. [PubMed: 20190640]
120. Creed TJ, Norman MR, Probert CS, Harvey RF, Shaw IS, Smithson J, et al. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther*. 2003 Jul 1; 18(1):65–75. [PubMed: 12848627]
121. Feist E, Burmester GR. Canakinumab for treatment of cryopyrin-associated periodic syndrome. *Expert Opin Biol Ther*. 2010 Nov; 10(11):1631–6. [PubMed: 20955115]
122. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003 Mar; 22(2):151–85. [PubMed: 12606142]
123. Kempen JH, Gangaputra S, Daniel E, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, et al. Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. *Am J Ophthalmol*. 2008 Dec; 146(6):802–12. e1. [PubMed: 18579112]

Table 1

Drugs Commercially Available for the Treatment of Uveitis.

Drug	Company	Class	Mechanism of action	Dosing
Prednisone	Multiple, generic	Glucocorticoid	Multiple mechanisms	Varies, see text
Triamcinolone	Apothecon, generic	Glucocorticoid	Multiple mechanisms	Periocular 20–40 mg; Intravitreal 1–4 mg in 0.1 ml
Flucinolone acetonide implant ^I	Bausch and Lomb	Glucocorticoid	Multiple mechanisms	0.59 mg implant for 30 months
Dexamethasone intravitreal implant ^I	Allergan Inc.	Glucocorticoid	Multiple mechanisms	0.7 mg for up to 6 months
Bevacizumab	Genentech	Anti-VEGF	Blocks VEGF	Intravitreal injection of 1.25 mg monthly
Ranibizumab	Genentech	Anti-VEGF	Blocks VEGF	Intravitreal injection of 0.5 mg monthly
Azathioprine	Glaxo Smith Kline, generic	Antimetabolite	A purine nucleoside analog that interferes with DNA and RNA synthesis	2–2.5 mg/kg/day or 150 mg/day
Methotrexate	Teva Pharmaceutical Inc., generic	Antimetabolite	Inhibits dihydrate folate reductase	7.5–25 mg per week given with folic acid
Mycophenolate mofetil	Roche, Novartis, generic	Antimetabolite	Inhibits ionisine monophosphate dehydrogenase	500–1500 mg bid
Cyclosporine	Novartis, Abott Laboratories, generic	T cell inhibitor	Calcineurin inhibitor	3–5 mg/kg/day in divided doses
Tacrolimus	Astellas Pharma Inc., generic	T cell inhibitor	Calcineurin inhibitor	0.05 mg/kg/day
Sirolimus	Wyeth, generic	T cell inhibitor	Inhibits mTOR pathway	Loading dose of 6mg followed by 2 mg per day
Cyclophosphamide	Bristol-Myers Squibb, generic	Alkylating agent	DNA cross-linking	1–3 mg/kg
Chlorambucil	Glaxo Smith Kline, generic	Alkylating agent	DNA cross-linking	Long term: 0.1–0.2 mg/kg; short term: 2 mg/day for 1 week followed by 2 mg per week
Infliximab	Centocor Ortho Biotech	Biologic	Anti-TNF α	3–10 mg/kg infusions at 0, 2, 6, 8 weeks and then every 4 to 8 weeks
Adalimumab	Abott Laboratories	Biologic	Anti-TNF α	40 mg subcutaneous injection every 1–2 weeks
Etanercept	Immunex Corp.	Biologic	Anti-TNF α	25 mg subcutaneous injection 1–2 times weekly
Daclizumab	Hoffman-La Roche Inc.	Biologic	Blocks IL-2 receptor (CD25)	1–2 mg/kg every 2–4 weeks
Interferon α 2a	Hoffman-La Roche Inc., generic	Biologic	Anti-immunomodulatory effects	3–9 million units once daily–thrice weekly

Drug	Company	Class	Mechanism of action	Dosing
Rituximab	Genentech Inc.	Biologic	Anti-CD20	1000 mg given twice at 2 week intervals

¹ Both flucinolone acetonide implant and dexamethasone intravitreal implant are currently the only FDA approved drugs for uveitis. Other medications listed are used as part of standard of care.

Table 2
Potential compounds for the treatment of uveitis(*information gathered through clinicaltrials.gov*)

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
AIN457	Novartis	Monoclonal antibody	Uveitis Psoriasis Other inflammatory conditions	Phase 3	Inhibits IL-17
Aprenilast	Celgene	Selective cytokine inhibitor	Uveitis Psoriasis	Phase 1 and 2	Inhibits TNF- α , Phosphodiesterase IV, regulates neutrophil function, and has anti-angiogenic activity
Voclosporin (LX-211)	Lux Biosciences	Analog of cyclosporin A	Uveitis Psoriasis Transplant rejection	Phase 3	Calcineurin inhibitor
ESBA-105	Alcon	Monoclonal antibody	Uveitis AMD, PVR, CME Rheumatologic inflammatory conditions	Phase 2	Inhibits TNF- α
Dexamethasone phosphate (EGP-437)	EyeGate	Corticosteroid	Anterior uveitis Corneal graft rejection Dry Eye	Phase 1 and 2	Glucocorticoid
MM-093	Merrimack	Recombinant human α -fetoprotein	Sarcoid or birdshot uveitis Myasthenia Gravis	Phase 2	Immunomodulator
Basiliximab	Novartis	Monoclonal antibody	Transplant rejection Inflammatory bowel disease	Approved	Inhibits IL-2
Everolimus	Novartis	Macrolide	Transplant rejection Cancer	Approved	mTOR inhibitor
Canakinumab	Novartis	Monoclonal antibody	CAPS, NOMID	Approved	Inhibits IL-1 β