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REVIEW

Immunosuppressive Treatment of Non-infectious Uveitis: History and Current Choices

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Abstract Non-infectious uveitis is one of the leading causes of preventable blindness worldwide. Long-term immunosuppressive treatment is generally required to achieve durable control of inflammation in posterior and panuveitis. Although systemic corticosteroids have been the gold standard of immunosuppressive treatment for uveitis since first introduced in 1950s, its side effects of long-term use often warrant an adjuvant treatment to reduce the dosage/duration of corticosteroids needed to maintain disease control. Conventional immunosuppressive drugs, classified into alkylating agent, antimetabolites and T cell inhibitors, have been widely used as corticosteroid-sparing agents, each with characteristic safety/tolerance profiles on different uveitis entities. Recently, biologic agents, which target specific molecules in immunopathogenesis of uveitis, have gained great interest as alternative treatments for refractory uveitis based on their favorable safety and effectiveness in a variety of uveitis entities. However, lack of large randomized controlled clinical trials, concerns about efficacy and safety of long-term usage, and economic burden are limiting the use of biologics in non-infectious uveitis. Local administration of immunosuppressive drugs (from corticosteroids to biologics) through intraocular drug delivery systems represent another direction for drug development and is now under intense investigation, but more evidences are needed to support their use as regular alternative treatments for uveitis. With the numerous choices belonging to different treatment modalities (conventional immunosuppressive agents, biologics and local drug delivery systems) on hand, the practice patterns have been reported to vary greatly from center to center. Factors influence uveitis specialists' choices of immunosuppressive agents may be complex and may include personal familiarity, treatment availability, safety/tolerability, effectiveness, patient compliance, cost concerns and suggestions from related specialists such as rheumatologists and pediatricians. The focus of this review is to provide an overview of each treatment modality on safety/tolerability and effectiveness, which are believed to be the two most important factors affecting treatment decision making.

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INTRODUCTION of corticosteroids in early 1950s opened a new era of anti-inflammatory treatment for ocular inflammatory diseases.¹⁻² Despite the favorable therapeutic results in early observations, corticosteroids were soon reported to induce increased intraocular pressure³⁻⁴ and posterior subcapsular cataract,⁵ and were later found to cause unintended side effect in any structure of the eye.⁶ Systemic toxicities secondary to long-term immunosuppressive treatment with corticosteroid are even more formidable and may result in morbidities in multiple organ systems or even death.⁷⁻⁸ Immunosuppressive agents, classified into alkylating agents, including cyclophosphamide (CTX) and chlorambucil (CHB); antineoplastic agents, including azathioprine (AZA), methotrexate (MTX) and mycophenolate mofetil (MMF); and T cell inhibitors, including cyclosporine A (CsA) and tacrolimus (FK506),⁹⁻¹⁰ were later introduced into treatment of ocular inflammation, with the earliest reports date back to late 1960s.^{9, 11} Initially, concerns about the low therapeutic index of immunosuppressive agents limited their use to the treatment of corticosteroid resistant or intolerant, or sight-threatening cases.¹¹⁻¹² Equipped with improved knowledge on drug pharmacological mechanism and drug toxicity, as well as increased clinical experiences, immunosuppressive agents gradually gained recognition as the treatment of choice for a number of ocular inflammatory diseases.¹² When administered at properly adjusted doses and by experienced physicians with close monitoring, immunosuppressive agents appeared to produce fewer adverse effects than chronic use of systemic corticosteroids.¹² They now have been widely used as complementary treatments in settings when (1) corticosteroids are insufficient to control the disease (recalcitrant), (2) long-term immunosuppression is needed to achieve disease control but expected corticosteroid toxicity is high at dose required (greater than 10 mg/d), which is often the case for treatment of uveitis, or (3) contradictions to high-dose (or long-term use) of corticosteroids are present.^{9, 13-14} Selected diseases, such as Behcet's disease with posterior segment involvement and mucous membrane pemphigoid with ocular involvement, are candidates for immunosuppressive drug therapy from the onset because of their poor natural history.⁹

Despite the above mentioned advances, challenges remain at least in the following aspects for conventional cytotoxic immunosuppressive agents. Firstly, some diseases such as birdshot chorioretinopathy, juvenile idiopathic arthritis-uveitis and serpiginous choroiditis respond poorly to these medications, even with combination therapy at maximum therapeutic doses.¹⁰ Secondary, even in most

experienced tertiary centers, corticosteroid-sparing success (sustained control of inflammation while tapering prednisone to 10 mg or less among those not meeting success criteria initially) was gained by 60%-70% of patients with ocular inflammation for CTX¹⁵ and AZA,¹⁶ and by 36% for CsA,¹⁷ in a period of 12 months, suggesting the limited role of "corticosteroid sparing" for those most commonly used immunosuppressive drugs with regard to the whole patient population. Thirdly, macular edema, which can cause profound visual loss and is one of the major causes of legal blindness in patients with uveitis, may become refractory to all currently available immunosuppressive drugs.¹⁸

Biologics act as selective suppressors of immune responses by targeting specific molecules in effector mechanisms of autoimmunity and inflammation; they can be recombinant antibodies to, or antagonists of, particular cytokines or cell-surface receptors, and recombinant cytokines [such as interferons (IFNs)].¹⁹ Since first reported in 1994,²⁰ a number of biologics have been investigated for their role in management of ocular inflammation, with majority of the publications related to uveitis.²¹ Reported biologic agents for non-infectious uveitis include tumor necrosis factor (TNF) inhibitors (infliximab, etanercept and adalimumab), anti-interleukine (IL)-1 β monoclonal antibody (gevokizumab), anti-IL-2R monoclonal antibody (daclizumab), anti-IL-6R monoclonal antibody (tocilizumab), anti-IL-17A antibody (secukinumab), anti-CD20 monoclonal antibody (rituximab), anti-CD52 monoclonal antibody (alemtuzumab), fusion protein of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (abatacept) and IFNs (IFN- α and IFN β).^{19,22} Biologics provide new hopes for the treatment of refractory uveitis and currently available evidences have shown a favorable safety and efficacy profile for most of the biologic agents.²²⁻²³ A continuous emerging of new biologic agents into the armory of uveitis specialists for combating ocular inflammation, mainly from that of rheumatology colleagues, is expected. However, lack of large randomized controlled clinical trials, concerns about efficacy and safety of long-term usage, and economic burden of the patients and the society, which is perhaps the biggest limiting factor even in developed countries,²³⁻²⁴ have limited the usage of biologics in non-infectious uveitis.

As systemic side effects are one of the major concerns for immunosuppressive treatment in uveitis, local administration of corticosteroids, conventional immunosuppressive drugs, as well as biologics represent another direction of drug development for uveitis.²⁵ Routes of local ocular drug administration used in uveitis include topical application, sub-conjunctival or sub-tenon injection, periocular (including

orbital floor and posterior sub-tenon injection), and intravitreal route (injection or implant).²⁵⁻²⁹ While topical corticosteroids are generally used for treatment of anterior uveitis, they are inadequate to reach therapeutic concentration in ocular compartments beyond the lens.³⁰ Subconjunctival or sub-tenon injection are effective method for delivering corticosteroids into both the anterior and posterior segments of the eye, and peri-ocular injections are thought to be more effective for posterior segment inflammation particularly for macular edema.²⁸ Although local administration techniques spare the patients systemic side effects of corticosteroids, ocular complications particularly cataract and glaucoma are unavoidable. Immunosuppressive drugs and biologics, as well as non-steroidal anti-inflammatory drugs, have come on the scene as candidates and might be the future trend for development of local treatment for uveitis.²⁵

A search of the reviews regarding treatments of uveitis published in different years not only reveals the developmental history of, but also provides state-of-the-art references and guidelines for, medical treatments of non-infectious uveitis.^{9-10, 12, 21, 25, 31-35} Thus this article is not a systemic review of all of the currently available immunosuppressive treatment modalities for uveitis, but try to provide basics for treatment decision-making in different clinical settings in this particular area.

CORTICOSTEROIDS

Corticosteroids have been the mainstay and the gold standard for treatment of uveitis.²⁸ The advantages of corticosteroids are their quick immunosuppressive action, low cost as compared with other treatment modalities, and the acute complications are of less concern.^{7, 14, 28} Generally, topical corticosteroids are sufficient to control most cases of anterior uveitis, and systemic corticosteroids are indicated for posterior uveitis and panuveitis.¹ For idiopathic intermediate uveitis, periocular corticosteroids are first line treatment indicated by decrease of visual acuity to <20/40 due to macular edema, vitreous haze and retinal vasculitis, with oral corticosteroids serving as the second line treatment for unresponsive or bilateral severe diseases.³⁶ The major concern of corticosteroids, however, is their ocular and systemic side effects of long-term use.⁹ Generally initial high-dose oral corticosteroids are continued for no longer than 1 month before commencement of tapering, and long-term maintenance dosage should be less than 10 mg per day of prednisone or its equivalent.⁹ Close monitoring of the potential side effects should also never be underemphasized.⁹ Actually, concerns about

safety of corticosteroids expressed by uveitis specialists were so strong that "corticosteroid-free" has been one of the major goals for future developments.¹⁴

On the other hand, however, corticosteroids are still irreplaceable in the foreseeing future for ocular inflammatory diseases²⁸ as well as in other medical fields such as asthma.³⁷ Thus, development of new corticosteroids which are well situated to separate local anti-inflammatory activity from systemic side effects (soft corticosteroids) using the 'retrometabolic design' technique remains to be an important goal of drug designers.^{2, 38-39} Loteprednol etabonate³⁹ and rimexolone⁴⁰ were developed by this approach and have been shown to be less glaucoma-causative. In our clinical practice, Lotemax (0.5% Loteprednol Etabonate Ophthalmic Suspension, Bausch & Lomb, Inc., Rochester, New York, USA) was often used as substitute for Pred Forte (1% Prednisolone Acetate Ophthalmic Suspension, Allergan, Inc., Irvine, CA, USA) in patients who are at risk for or with present corticosteroid induced glaucoma.

CONVENTIONAL IMMUNOSUPPRESSIVE AGENTS

The key role of immunosuppressive agents, which can conveniently be grouped as alkylating agents, antimetabolites and T cell inhibitors, is "corticosteroid-sparing", when long-term immunosuppression is needed. Since they are not potent instant inhibitors of the immune system and usually require several weeks to take effect, they were usually co-administered with large dose oral corticosteroids in acute phase of severe ocular inflammation. With the aid of immunosuppressive drugs, a lower level of corticosteroids, or even none if possible, is expected to be needed for chronic control of diseases than corticosteroid alone. In another word, when in combination with immunosuppressive drugs, more patients could be controlled at low dose of corticosteroids with minimal side effects.⁹ In patients who are refractory to corticosteroid treatment, immunosuppressive drugs may play a bigger role in inflammation control³¹ and may sometimes even serve as a rescue therapy.⁴¹⁻⁴²

Immunosuppressive agents have historically been introduced into clinical practice of uveitis with reference to their success in controlling other autoimmune inflammatory disorders and transplant rejection,^{14, 43} and in the field of ocular inflammation, almost all are used off-label.⁴³ Although there has been a large body of evidences showing the advantages of immunosuppressive drugs in treatment of uveitis, indications for selection of one immunosu-

ppressive agent *versus* another are still unknown,⁴⁴⁻⁴⁵ since most of the published evidences are weak observational case series with a lack of randomized controlled clinical trials which compare different immunosuppressive drugs in different uveitis entities.⁴⁵ Thus, practice patterns in immunosuppressive treatment may vary greatly from center to center in China. For example, in a tertiary uveitis center (Dr Peizeng Yang's group) in south China, CHB and CsA were the most frequently used immunosuppressive drugs in patients with Vogt-KoyanagiHarada disease (VKH)⁴⁶ or Behcet's disease.⁴⁷ In our center, however, CsA, or occasionally CTX or AZA, was used in accordance with international experiences.⁴⁸

Factors influence uveitis specialists' choices of immunosuppressive agents may be complex and may include one's personal familiarity, treatment availability, safety/tolerability, effectiveness, patient compliance, cost concerns and suggestions from related specialists such as rheumatologists and pediatricians.^{45, 49} A recent survey of members of the American Uveitis Society revealed that the majority of respondents preferred MTX as their first choice among the corticosteroid-sparing agents for non-infectious uveitis in all three anatomic subgroups (anterior, intermediate, posterior/panuveitis), followed by MMF.⁴⁵ The two most important factors affecting decisions of the respondents were safety/tolerability and effectiveness, despite other factors were also involved.⁴⁵ The following paragraphs will focus on safety and effectiveness profiles of the most commonly used immunosuppressive drugs, which have been figured out by currently available information, especially those from a recent series of large retrospective cohort studies^{15-17, 44, 50} and a few retrospective or prospective comparative studies.^{49, 51-52} These evidences should not be underestimated for their role in optimizing our use of corticosteroid-sparing agents.⁴³

Alkylating agents

Alkylating agents are believed be effective for most forms of ocular inflammation and have the advantage of inducing a high rate of medication-free remission after treatment.^{33, 35, 45} Both CHB^{15, 53-56} and CTX⁵⁷⁻⁶⁰ had been successfully used in patients with a variety of severe or even recalcitrant ocular inflammatory diseases. However, the risk of side effects is substantially greater than that associated with alternative agents and requires very careful monitoring.¹⁵ The major side effects of alkylating agents were bone marrow suppression, hemorrhagic cystitis, gonadal dysfunction and an increased risk of malignancy,^{9, 45, 61} with common minor side effects such as fatigue, nausea, vomiting, alopecia and headache.^{9, 59} Other possible side effects

include cardiac myopathy, hepatic dysfunction, and irreversible pulmonary fibrosis.⁶¹ While most of the side effect profile overlap between the two alkylating agents, CHB can be associated with unpredictable and sudden pancytopenia, many clinicians prefer to use CTX.⁵⁹ However, CTX can cause severe hemorrhagic cystitis and when it happens, CHB may be used as a replacement.⁹ All patients on CTX therapy should be encouraged to drink two or more liters of fluid per day to minimize bladder toxicity.⁹ Both younger and older patients (older than 65 years) need special attention when on alkylating agents; for the former group, fertility preservation might be important, and for the latter, bone marrow suppression occurs more often.⁹

With the advent of newer immunosuppressive drugs, alkylating agents is now the least preferred category of conventional immunosuppressive drugs in the United States⁴⁵ and is suggested to be reserved for severe or recalcitrant cases of ocular inflammation.¹⁵

T cell inhibitors

CsA

CsA was first successfully used by Nussenblatt and coworkers to treat poorly controllable uveitis in 1983.^{41, 62} At an initial dose of 10 mg/kg·d, it was later reported to be able to control severe uveitis of a variety of causes such as Behcet's disease, birdshot chorioretinopathy, sarcoidosis, pars planitis, Vogt-Koyanagj-Harada disease, sympathetic ophthalmia, and idiopathic uveitis could be controlled.^{51, 63-66} In a case series of 52 patients, 41 (79%) patients were therapeutically successful at three months after the initiation of CsA as the sole systemic immunosuppressive agent for their disease. Twenty-five of a potential 35 (71%) patients remained on CsA after one year's time, with 63% (22/35) of these individuals considered a therapeutic success.⁶³ In a randomized, controlled clinical trial of 56 patients with uveitis, CsA was found to be similar to oral corticosteroids in terms of efficacy.⁶⁷ In another double-masked controlled trial, CsA at this dosage (10 mg/kg·d) was found to be superior to CHB (1 mg per day) in the treatment of the ocular complications of Behcet's disease.⁵¹ However, adverse reactions, mainly renal toxicity and hypertension, required a reduction in CsA dosage or stop in a significant portion of patients, suggesting that CsA is not suitable for long-term inflammation control at high dosage as a single agent.⁶³ Thus, CsA with lower doses (5 mg/kg·d or less), mainly used as an corticosteroid-sparing agent, was later tried in hopes of achieving similar antiinflammatory results with less toxicity.⁶⁸⁻⁷¹ This lower dosage, 2 to 5 mg per kg per day, at which a much lower rate of nephrotoxicity had been

observed, is currently suggested for ocular inflammatory diseases in a recent guideline with wide consensus.⁹ However, in a uveitis cohort study of at least 2 years of follow-up, long-term CsA therapy with even low dosage appeared to be nephrotoxic and is associated with a high incidence of hypertension.⁶⁹ Careful monitoring serum creatinine (every 2 weeks initially and monthly once dosage has stabilized) is mandatory to detect significant change in renal function before irreversible damages happen.⁹ The patient's blood pressure should be checked at every visit and no less frequently than monthly initially and every 3 months for patients on long-term therapy.⁹ At the currently suggested dosage, CsA was found to be moderately effective in inflammation control and accomplishing corticosteroid-sparing goals; it is relatively safe in younger patients, but treatment limiting toxicities (renal toxicity and hypertension) are frequent among patients ages 55 years and older.¹⁷ Less commonly encountered side effects include hypercholesterolemia, hepatotoxicity, gingival hyperplasia, myalgia, tremor, paresthesia, hypomagnesemia, and hirsutism.⁹

Tacrolimus

Tacrolimus, or FK506, is a macrolide antibiotic synthesized by the bacterium *Streptomyces tsukubaensis*. FK506 and CsA share a common pathway for immunosuppression by inhibits T-cell activation through inhibition of calcineurin, which is required for the induction of T cell lymphokine production (IL-2) during T cell activation.⁷² FK506 was first applied to control refractory uveitis in Japan with a favorable efficacy profile,⁷³⁻⁷⁴ and later proved to be successful in patients refractory to CsA.⁷⁵ A more recent long-term retrospective observational case series demonstrates favorable long-term clinical efficacy with excellent tolerability.⁷⁶ Another report provides preliminary evidence that corticosteroids can be withdrawn in FK506 treated patients who are able to achieve control of posterior segment inflammation with 10 mg prednisone daily.⁷⁷ While the side-effect profile of FK506 is similar to that of CsA, incidence of intolerable side effects at therapeutic dosage is believed to be lower than that of CsA.⁹

Voclosporin & sirolimus

Voclosporin is a new-generation calcineurin inhibitor and has been put on a series of three randomized, double-blind, placebo-controlled, phase II/III trials as an alternative to CsA.⁷⁸ The limited data available indicate at least comparable results relative to current therapy with a better safety profile.⁷⁹ However, future researches are needed to establish the necessity of adding this new drug into the

arsenal of uveitis treatments.⁶¹ Sirolimus (rapamycin) is not a calcineurin inhibitor, but also acts as a potent inhibitor of T cell activation through a pathway involving mammalian target of rapamycin (mTOR).⁸⁰ There is also little experience with this drug, but small case series have suggested it may be useful in uveitis patients.⁸¹⁻⁸² It has also been selected as a candidate for development of local treatments.⁸³⁻⁸⁴

Antimetabolites

MTX

Since first reported in 1965, a number of case series have reported MTX to be effective for treatment of non-infectious uveitis,^{44, 50} including specific uveitis entities such as juvenile idiopathic arthritis-associated uveitis,^{31, 85} Behcet's disease,⁸⁶ sarcoidosis-related panuveitis,⁸⁷ and sympathetic ophthalmia.⁸⁸ In a large observational case series⁸⁹ and a multicenter retrospective cohort study,⁵⁰ MTX was found to be moderately effective, but it is likely to be well tolerated with important long-term adverse effects to be rare when closely monitored; and when side effects do occur, they are likely to be reversible.^{50, 89} The favorable safety profile might explain why it has been the first choice among uveitis specialists in the United States.⁴⁵ MTX, however, was the only drug in which there was a significant difference in effectiveness ratings by anatomic location of inflammation,⁴⁵ with treatment success achieved most common in patients with anterior uveitis and scleritis.³⁵ One feature of this drug worth mention here is its slow rate of onset of effect, with many patients requiring 6 months of therapy to achieve full corticosteroid-sparing effect.⁵⁰ Bone marrow suppression is the major dose limiting factor when administering MTX therapy.^{4, 50} Hepatotoxicity is another serious side effect for MTX with elevation of liver enzymes observed in about 15% of treated patients.⁹⁰ Thus, close monitoring of liver function was suggested and the patients need to refrain from alcohol consumption.⁹⁰ The authors of this current review suggest that special attention should be paid to patients with hepatitis B, which is a relatively common hepatic disease in China. Pretreatment abnormality of liver enzyme level in patients with hepatitis B may warrant instant hepatoprotective treatment and closer monitoring of liver function. Gastrointestinal intolerance (nausea, ulcerative mucositis, and diarrhea) represents another common cause of drug discontinuation in uveitis patients, but the clinical significance is of less a concern.^{50, 61} Pulmonary toxicity manifested as acute pneumonitis is an uncommon but life-threatening side effect of MTX, and resolution usually occurs after discontinuation of therapy and high dose corticosteroid treatment.⁹¹ Other reported

side effects with MTX include renal failure, cutaneous vasculitis, urticaria, photosensitivity, alopecia, and cutaneous nodules.^{35, 61}

AZA

AZA, since first used in ocular inflammation in 1996, has been shown to be effective in the management of various corticosteroid-resistant ocular inflammatory diseases, particularly scleritis secondary to relapsing polychondritis, ocular cicatricial pemphigoid, juvenile idiopathic arthritis associated iridocyclitis and intermediate uveitis. However, efficacy of AZA on other uveitis entities such as sympathetic ophthalmia and Behcet's disease were inconsistent.^{35, 61} In a large retrospective cohort, AZA was reported to have comparable overall efficacy to CsA and MTX, but the treatment-limiting toxicities, although nearly all would be detectable and reversible, are relatively common.¹⁶ In accordance with previous reports, a significantly better response of patients with intermediate uveitis to AZA than anterior uveitis, with 89.8% achieving complete control of inflammation sustained for at least 28 days and 68.2% meeting corticosteroid-sparing objectives before 12 months of therapy, were observed in this study.¹⁶ In this cohort, the most common side effect of AZA is gastrointestinal upset, which caused drug intolerance in approximately 9% patients during a median follow-up of 230 days.¹⁶ Myelosuppression and hepatic toxicity were other two major side effects causing drug discontinuation, in 5% and 4% of patients, respectively.¹⁶ Myelosuppression typically develops 1 to 2 weeks after initiation of treatment, and are usually reversible upon discontinuation.⁹² Patients with homozygous deficiency in the thiopurine S-methyltransferase (TMPT) gene locus, occurring in approximately 1 of 300, are extremely sensitive to AZA induced myelosuppression and is life-threatening when exposed to this drug.⁹³ Uveitis specialists should also be familiar with the interactions between allopurinol and AZA, which can lead to severe myelosuppression or even death; and when intentional co-prescription of AZA and allopurinol is indicated, the AZA dose must be reduced to 25%-33% of the normal dose with careful hematological monitoring thereafter.⁹⁴ Other known side effects, albeit less common, include secondary infection, interstitial pneumonitis, pancreatitis, stomatitis, and alopecia.^{35, 61} One point worth mention here is that current evidence for safety of AZA (50-100 mg/d) during pregnancy may substantiate it a good choice for pregnant women.⁹⁵⁻⁹⁶

MMF

MMF is a relatively new immunosuppressive drug with its

debut on the stage of uveitis in 1998.⁴² Despite its limited experiences in practice of uveitis, this drug has gained considerable popularity, reflected by the emerging publications on its effectiveness in this particular field,^{44, 97-103} as well as its second priority among uveitis specialists' current choices of immunosuppressive drugs in the United States.⁴⁵ Being used alone or in combination with other steroid-sparing immunosuppressive drugs, MMF has been reported to be effective for uveitis in both children^{97, 101} and adults, at different locations of the uvea (anterior, intermediate, posterior/panuveitis),^{44, 104-105} as well as specific entities including sarcoidosis⁹⁹ and VKH.¹⁰³ In the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, the efficacy and safety profiles of MMF as the single initial corticosteroid sparing immunosuppressive agent were unremarkable with reference to alternative immunosuppressive drugs used in this same cohort, but a good long-term tolerance rate as with MTX, was observed.⁴⁴ In this report, prior treatment with alkylating agents was associated with a 70% reduction of likelihood of treatment success, while prior exposure to different antimetabolites was not.⁴⁴ Actually, in another report, about half of the patients who had previously failed with or did not tolerate MTX were effectively controlled by changing to MMF, suggesting that MMF is a reasonable next step for patients failing MTX.⁹⁸ In a retrospective study which compared efficacy/safety between MTX, MMF and AZA, MMF appeared to be able to achieve control of ocular inflammation faster than MTX or AZA, and AZA had a higher rate of treatment-related side effects in comparison with the other two agents.¹⁰⁶ Despite data showing advantages of MMF over the other two antimetabolites are accumulating, currently there is a lack of high-level evidences. Results of an on-going clinical trial which compares MTX and MMF in the clinical setting of uveitis [the Methotrexate and Mycophenolate Mofetil for UVEITIS (FAST) study, www.clinicaltrials.org] may fill this gap in the near future. Side effects of MMF are minimal and cause discontinuation of treatment in about 12% of patients in the first year and rare thereafter, with gastrointestinal upset, bone marrow suppression and hepatotoxicity being the major treatment limiting factors.⁴⁴ Other reported side effects include headache, malaise, allergy, myalgia, dizziness, chest pain and hair loss.^{44, 104-105}

BIOLOGICS

The development of biologics has provided uveitis specialists with a variety of new treatments for refractory uveitis patients who are resistant to conventional corticosteroid

and immunosuppressive treatments. Since some state-of-the-art reviews on this topic are available,^{19, 21, 22, 34, 107} we are not going to elaborate details of this new treatment modality, but try to summarize the indications for, and overall safety and effectiveness profiles of, currently available biologic agents which has been used in the clinical practice of uveitis.

Anti-TNF-alpha agents

The first reports on efficacy of anti-TNF- α agents in treating uveitis were published in 2001.¹⁰⁸⁻¹¹¹ Inspired by the exciting results of infliximab on long-standing panuveitis in Behcet's disease,^{108, 110} there had been a rapid increase in interest for the role of infliximab on this special entity.²¹ The consistency of the positive response in the reports emerged in the next few years led infliximab to be considered as the "gold standard" for Behcet's disease uveitis by some authors.¹¹² The success of infliximab has also been found in a variety of other uveitis entities refractory to conventional immunosuppressive treatment, including sarcoidosis, VKH, idiopathic uveitis, uveitis associated with ankylosing spondylitis and pediatric uveitis.¹¹³⁻¹²¹ While favorable short-term results were observed in most of the published reports with little toxicity, the effect is temporary and repeated infusions are necessary every 4-8 weeks to maintain remission.^{19, 21} The risk of treatment failure, however, has been found to be significantly correlated with the duration of treatment and with the total number of infusions;²² this might be explained by the development of antibodies against the murine component of the molecule.²¹⁻²² Long-term infliximab therapy may also induce several serious side effects including an increased risk of malignancies, congestive heart failure, tuberculosis, optic neuritis, multiple sclerosis, and lupus-like reactions, therefore treatment of infliximab should be avoided in patients with positive history of these conditions.^{19, 22} A recent publication showed that an increase of serum titer of antinuclear antibodies (ANA) might be associated with therapeutic efficacy in the treatment of Behcet's disease.¹²²

The clinical results of etanercept, however, have not been so consistent since the beginning.^{109, 111} A search of the literature has revealed reports with both favorable¹²³⁻¹²⁵ and discouraging results¹²⁶⁻¹²⁷ with regard to its efficacy in the treatment of uveitis. In some retrospective comparative studies, etanercept appeared to be inferior to infliximab in controlling recalcitrant uveitis.¹²⁸⁻¹²⁹ In a recently published large-scale cohort study, patients under etanercept monotherapy developed more frequently incident uveitis than patients treated by etanercept in combination with

MTX or MTX alone.¹³⁰ In addition, "*de novo*" induction or exacerbation of uveitis has been reported in the literature during treatment of etanercept,¹³¹⁻¹³² casting more shadow on its usage in uveitis.

Adalimumab is a relatively new anti-TNF- α antibody with first reports in uveitis appeared in 2006.¹³³ It is a kind of humanized recombinant IgG1 anti-TNF- α monoclonal antibody, and as compared with infliximab, adalimumab has the technical advantage of a subcutaneous administration.¹³⁴ Currently, the efficacy of adalimumab has been established in the literature with positive reports covering a variety of uveitis entities (categories).^{133, 135-142} Several studies have compared infliximab and adalimumab in the treatment of uveitis and the latter appears to have better long-term efficacy and safety/tolerance profiles.^{135, 143-144} Adalimumab has also been reported as a successful second line treatment for patients failing infliximab.^{139, 145} The side effect profile of adalimumab is similar to that of infliximab, except for the local injection site reactions, which is actually the most common side effect.¹⁴⁶

IFN- α

IFN- α is a naturally occurring cytokine secreted in response to viral infections, primarily by plasmacytoid dendritic cells. In addition to its anti-viral effect, IFN- α has immunomodulatory effects, and was believed to be a key mediator of "systemic" autoimmune diseases such as systemic lupus erythematosus (SLE), thyroiditis, and diabetes mellitus, while TNF- α is prominent as the pathogenetic cytokine of "organ-specific" diseases such as rheumatoid arthritis and multiple sclerosis.¹⁴⁷ It has been suggested that cross-regulation between IFN- α and TNF- α operates in the healthy state and that imbalance of either would induce either systemic, or organ-specific autoimmune diseases.¹⁴⁷ Uveitis is believed to be in the category of organ specific autoimmune disease thus, either blocking of TNF- α , or enhancement of IFN- α , may suppress the disease activity.¹⁴⁸ Both recombinant human IFN- α 2a and IFN- α 2b have been successfully used to treat posterior uveitis, with the majority of studies using IFN- α 2a and in the clinical setting of Behcet's uveitis,¹⁴⁹⁻¹⁵⁶ although several reports have also included patients with other causes of uveitis including idiopathic panuveitis, sympathetic ophthalmia, VKH, serpiginous choroiditis, birdshot chorioretinopathy, and intermediate uveitis.^{148, 157} The side effects of IFN- α have been described in almost every organ system, with flu-like symptoms, hematological toxicity, elevated transaminases, nausea, fatigue, and psychiatric sequelae among the most frequently encountered. While some of the side effects can be managed medically, many side-effects can only be

adequately handled by dose adjustment or cessation of treatment.¹⁵⁸ Fortunately, as evidenced by two recent reports, low dosage (3.0 MIU 3 times per week) IFN- α 2a seems to be adequate to achieve long-term effectiveness in the majority of patients with refractory Behcet's uveitis with a favorable tolerance profile.¹⁵⁵⁻¹⁵⁶

Other biologic agents

Biologic agents target specific molecules involved in the pathogenesis of diseases. Since the pathogenesis of autoimmune diseases is complex and may involve all stages of an immune response from the afferent arm to the efferent arm, all elements of the immune system (the native and the adaptive immune elements, the cellular and the humoral immune branches),¹⁵⁹⁻¹⁶⁰ all molecules in the networks of cytokines, chemokines, costimulatory molecules, cell adhesion molecules and oxygen-free radicals may serve as potential targets for biologic therapy.²² Recently a number of new biologic agents including gevokizumab,¹⁶¹ daclizumab,¹⁶²⁻¹⁶⁴ tocilizumab,¹⁶⁵⁻¹⁶⁶ secukinumab,¹⁶⁷⁻¹⁶⁸ rituximab,¹⁶⁹⁻¹⁷² alemtuzumab¹⁷³ and abatacept,¹⁷⁴⁻¹⁷⁶ have been investigated for their role in treatment of ocular inflammation, following their success in rheumatology; however, since only a few pilot studies of small or medium size are currently available, future researches are needed to establish clearer efficacy/safety profiles of these drugs as treatment options in treatment of non-infectious uveitis.

LOCAL TREATMENTS

Delivery of drugs into the eye through systemic routes is difficult since the eye is a small organ with inherent protective barriers (blood-retina barrier and blood-aqueous barrier), and systemic side effects are to some extent unavoidable, if there is any, when a certain drug reaches local therapeutic concentration.¹⁷⁷ On the other hand, the superficial anatomic location, clear optical media for direct visualization and multiple compartments for drug retaining represent advantages of local drug delivery for this special organ.¹⁷⁸ However, like those newer biologic agents discussed in the previous section, this treatment modality is now under intense investigation with insufficient evidences to qualify its general clinical applicability in the current stage. A recent review has dedicated itself to local treatment of ocular inflammatory disease, so in the current review, only a few comments on this novel treatment modality in uveitis are delivered.¹⁷⁹⁻¹⁸⁰

The Multicenter Uveitis Steroid Treatment (MUST) Trial is the first multicenter, randomized clinical trial designed to compare intravitreal fluocinolone acetonide implant

(Retisert, Bausch & Lomb, Inc, Rochester, New York) *versus* systemic therapy for management of intermediate, posterior and panuveitis.¹⁷⁹ The intravitreal implant used in this trial can achieve sustained stable release of fluocinolone acetonide over a period of longer than a year.¹⁷⁸ Over a follow-up period of 24 months, the intravitreal implant has been shown to be at least as efficient as systemic treatment in terms of final visual outcome with intravitreal implant which gained control of inflammation faster.¹⁸⁰ The authors of this current review believe that the significance of this clinical trial is far beyond the positive therapeutic results of the implant itself; it showed us the first time that an appropriate local treatment can be a substitute for the gold-standard in the treatment of posterior and panuveitis, i.e. systemic corticosteroids. An emerging of local drug delivery devices loaded with various immunosuppressive agents, primarily intravitreal implants, is expected in the near future.

FUTURE PERSPECTIVES

Detailed discussion of future perspectives on treatment of uveitis is beyond the scope of this review. The following aspects are believed to be the directions for future developments in treatment of uveitis, by the authors of this review: development of novel agents (novel immunosuppressive agents and biologics) with better tolerance/safety profile; local treatments administered by reliable local drug-delivery systems; combination of treatments with different side effect profiles to achieve good disease control with minimal risks; more individualized treatments; and development of objective assessments for treatment guidance. The current goal of immunomodulatory therapy in chronic uveitis, however, is durable (at least 2 years) control of intraocular inflammation with less or without, concomitant use of oral or topical steroids.¹⁸¹

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