Systemic immunosuppressive therapies for uveitis in developing countries

Hitesh Agrawal, Hien Doan[1], Brandon Pham[1], Amit Khosla[2], Manohar Babu[3], Peter McCluskey[4], Quan Dong Nguyen[1], Virender Sangwan[5], Subhakar Reddy, Sujata Sawhney[2], Mudit Tyagi

There are multiple approaches to inhibit inflammatory molecules and pathways in noninfectious uveitis. The cornerstone of local and systemic anti-inflammatory treatment is corticosteroid therapy. Corticosteroids remain the most potent and efficacious drugs for treating intraocular inflammation. However, their long-term use is limited by their medium- and long-term side effects, which are a major concern. The approach taken to limit corticosteroid side effects is to introduce steroid-sparing agents that suppress the inflammatory pathways and immune response differently than corticosteroids. There are several classes of such drugs that are affordable, effective, and generally well-tolerated. Relatively recently, an increasing range of biologic agents has become available to treat intraocular inflammation. However, the relatively expensive cost of these therapies limits their use in the developing world. This systemic review aimst to discuss the use of corticosteroids and different immunosuppressive regimens in the management of various uveitides.

Key words: Biologicals, corticosteroids, immunosuppression, inflammation, non infectious uveitis

Uveitis is a term that encompasses a number of inflammatory, infectious, and neoplastic disorders that can involve the uveal tract.[1] It can affect both adults and children. Although a rare disorder and classified as an orphan disease, uveitis is among the most common causes of blindness and is responsible for 10%–15% of blind registrations.[2] Because many of those affected are children or working-age adults, the years of potential vision loss and economic impact of each case of vision loss are higher, on average, than with eye diseases of the elderly.

The standardization of the uveitis nomenclature project (SUN) has greatly advanced our ability to accurately classify and describe uveitis in affected patients.[3] SUN classifies uveitis anatomically into anterior, intermediate, posterior, and panuveitis [Table 1].

Noninfectious anterior, intermediate, posterior, and panuveitis are commonly associated with systemic inflammatory diseases such as sarcoidosis, Adamantiades–Behçet's disease, Vogt–Koyanagi–Harada disease, HLA B27 related disorders, and uveitis associated with juvenile idiopathic arthritis apart from other immune-mediated, inflammatory systemic inflammatory conditions.[4]

The management approach to patients with uveitis is fundamentally based on careful clinical assessment. A careful thorough history and a detailed clinical examination of both the eyes is critical to determine the clinical phenotype of the uveitis, and whether there are any clinical symptoms or signs that suggest an associated systemic disease. Following this, targeted investigations are performed to rule in or rule out specific disorders. At a minimum, syphilis serology and a chest X-ray and Mantoux test to exclude tuberculosis, and serology for HIV are ordered for all patients with uveitis.[5] There is a wide range of investigations that target specific systemic diseases such as tuberculosis and sarcoidosis, and others such as multimodal ocular imaging that target clinical features of disorders such as serpiginous choroidopathy and occlusive retinal vasculitis.[5]

Treatment is individualized depending upon the diagnosis. Infectious uveitis is treated with antimicrobial drugs and judicious anti-inflammatory therapy.

Inflammatory and undifferentiated uveitis may be treated with topical, regional, or systemic anti-inflammatory therapy. Typically the unilateral disease is managed with local therapy whenever possible while the majority of those with bilateral involvement are treated with systemic therapy. It is common for patients on systemic therapy to require supplemental local therapy.

There are multiple approaches to inhibit inflammatory molecules and pathways in uveitis and other diseases. Fig. 1 illustrates the protean processes involved in inflammation as well as selected pharmacologic agents, from antimetabolites to biologics to other classes of inhibitors that are employed to inhibit various pathways.

L V Prasad Eye Institute, Hyderabad, Telangana, [2]Sir Ganga Ram Hospital, [5]Dr Shroff Charity Eye Hospital, NewDelhi, [3]Aravind Eye Institute, Salem, Tamil Nadu, India, [1]Byers Eye Institute, Palo Alto, CA, USA, [4]Save Sight Institute, Sydney NSW, Australia

Correspondence to: Dr. Mudit Tyagi, L V Prasad Eye Institute, Banjara Hills Road No 2, Hyderabad, Telangana, India. E-mail: drmudittyagi@gmail.com

Cite this article as: Agrawal H, Doan H, Pham B, Khosla A, Babu M, McCluskey P, *et al*. Systemic immunosuppressive therapies for uveitis in developing countries. Indian J Ophthalmol 2020;68:1852-62.
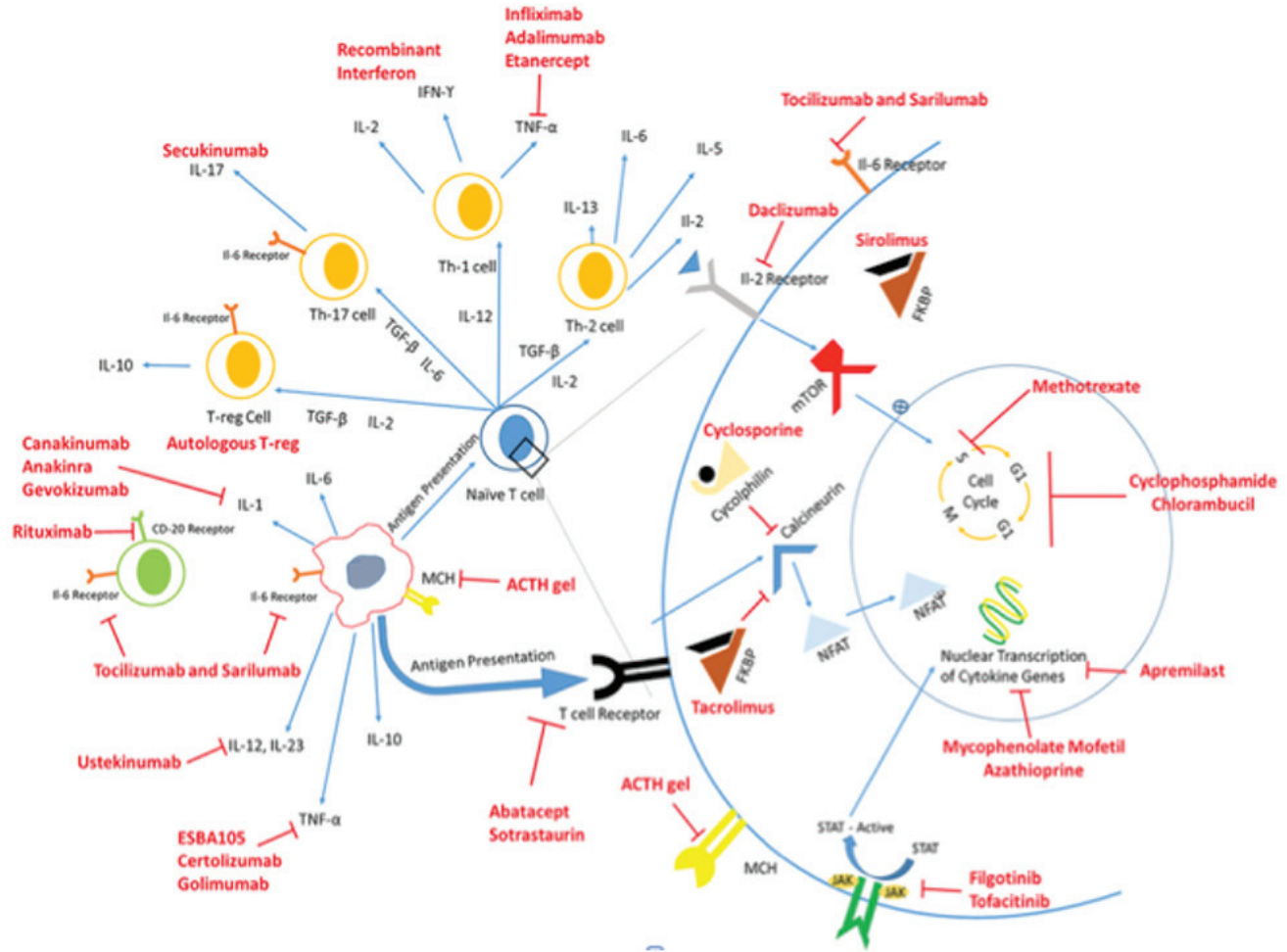
Figure 1: The protean processes that are involved in inflammatory diseases, including uveitis, as well as selected pharmacologic agents that are employed to inhibit various pathways

The cornerstone of local and systemic anti-inflammatory treatment is corticosteroid therapy. The use of corticosteroids for uveitis was first described in 1950 and even today, they remain the most potent and efficacious drugs for treating intraocular inflammation.[6-8] The challenge limiting corticosteroid use is their medium- and long-term side effects, which are a major concern for systemic corticosteroid therapy.[8] Currently, there are no curative therapies for noninfectious uveitis. The aim of treatment is to suppress the inflammation, causing the disease to regress over time and allowing therapy to be slowly tapered and discontinued. Some forms of uveitis require many years of immunosuppressive therapy.

Immunosuppressive drugs are used to treat many potentially blinding cases of ocular inflammation, primarily in 3 settings[7,8]
1. As corticosteroid-sparing therapy when the disease can be controlled with oral corticosteroids, but substantial toxicity is expected at the dose required
2. For inflammation that is recalcitrant to corticosteroids
3. For the management of specific diseases expected to fare poorly with corticosteroids alone.

The first described use of immunosuppression for uveitis was in 1951 when Roda Perez described the use of nitrogen mustard in treating steroid-resistant uveitis.[9]

Table 1: The SUN working group anatomic classification of uveitis[3]

Type	Primary cite of inflammation	Includes
Anterior	Anterior Chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate Uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior Uveitis	Retina or choroid	Focal, multifocal, diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

Over the past few years, immunomodulatory therapy (IMT) has become a standard part of our treatment regimen for uveitis and other ocular inflammatory diseases. These drugs are commonly used in combination with low-dose corticosteroids and/or other IMT agents.

The approach taken to limit corticosteroid side effects is to introduce steroid-sparing drugs that suppress the inflammatory pathways and immune response differently than corticosteroids.[7,8] There are several classes of such drugs that are affordable, effective, and generally well-tolerated. Relatively recently, an increasing range of biologic agents has become available to treat intraocular inflammation. However, the relatively expensive cost of these therapies greatly limits their use in the developing world.

This review aims to discuss the use of corticosteroids and different immunosuppressive regimens in the management of various uveitides.

Oral Corticosteroids

Corticosteroids are synthetic compounds that have both anti-inflammatory and immunosuppressive properties. They exert their anti-inflammatory action by their action on neutrophils: increased production, decreased migration to inflammatory sites, decreased adhesion to vascular endothelium, and decreased bactericidal activity. They exert their immunosuppressive effects by their action on mononuclear phagocytes (monocytes and macrophages) and T and B lymphocytes, namely inhibiting transcription of cytokines vital to chronic inflammation.[10]

Oral corticosteroids are considered to be the first-line treatment in controlling ocular inflammation. The initial dose of oral prednisolone is believed to be in the range of 1–1.5 mg/kg/day, which then needs to be tapered based on the extent of inflammation with the goal of achieving disease quiescence at a dose ≤7.5 mg per day.

No tapering is needed if a patient has been on systemic therapy for less than 7 to 14 days. If a patient has a completely suppressed hypothalamic pituitary adrenal axis (serum values of morning cortisol levels <10 mg/dL) or has been on the oral steroid for >6 months, replacement therapy (5–7.5 mg/day), or alternate day therapy (equivalent to the dose that would have been employed over a 48-h period) is mandatory [Table 2].

Intravenous corticosteroids

Methylprednisolone is an intermediate-acting steroid with anti-inflammatory activity similar to prednisolone but with no sodium retention. Used in pulsed intravenous therapy for rapid control of inflammation, it is recommended in severe sight-threatening ocular inflammatory conditions, such as necrotizing scleritis, Adamantiades–Behçet's disease, sympathetic ophthalmia, Vogt–Koyanagi–Harada disease, serpiginous choroiditis, optic neuritis, and others.

Dose- 500 mg^{-1} g pulses/day over 60 min in 100 mL normal saline × 3 days followed by the oral steroid.[10]

Adverse effects

1. Cushingoid changes (moon faces, weight gain, fat redistribution, acne)

2. Delay in pubertal growth in children below the age of 15 years
3. Diabetes mellitus (glucose levels should be monitored every 2–3 months in patients on long term corticosteroids)
4. Dyslipidemia.

Other less common adverse effects include impaired wound healing, increased risk of infections, glaucoma and cataracts, mood changes, and insomnia, among a very large list of potential adverse events.

Patients also need to be monitored for osteoporosis. The prevalence of glucocorticoid-induced avascular necrosis (AVN) is between 3% and 38%.[11]

Glucocorticoid-induced AVN most commonly affects the femoral head, but can also occur in knees, shoulders, ankles, and hands. Glucocorticoid-induced AVN accounts for about 10% of all cases of total hip replacement in the United States.[12] Therefore, careful inquiry about a history of painful joint movements is important.

It is also recommended to provide 1500 mg of calcium and 800 IU of vitamin D daily, in addition to replacing sex hormones if decreased or if postmenopausal to all patients on long-term oral corticosteroid therapy.[8]

While corticosteroids are the mainstay of treatment of noninfectious uveitis, their long-term use is associated with several adverse effects. Therefore, all patients who require chronic oral corticosteroid therapy may require immunosuppressive drugs or IMT.

Immunosuppressive Agents

1. Antimetabolites	Azathioprine
	Methotrexate
	Mycophenolate Mofetil
2. T-cell inhibitors	Cyclosporine
	Tacrolimus
3. Alkylating agents	Cyclophosphamide
	Chlorambucil

Antimetabolites

Antimetabolites are drugs that antagonize or compete with a metabolite, which is essential for nucleotide synthesis, leading to impaired cell division and proliferation. The three main antimetabolites used in the treatment of ocular inflammation are azathioprine, methotrexate, and mycophenolate mofetil.

Azathioprine

Azathioprine is a purine nucleoside analog that acts as an antimetabolite by interfering with deoxyribonucleic acid and ribonucleic acid synthesis. Azathioprine is a precursor to 6-mercaptopurine (6-MP), a purine analog competitive inhibitor of de novo purine synthesis, blocking DNA replication and RNA synthesis, thereby inhibiting the proliferation of actively dividing immune cells. Azathioprine decreases circulating lymphocytes, suppresses lymphocyte proliferation, and inhibits antibody production.

The bioavailability of azathioprine, as measured by 6-MP levels achieved after oral administration, varies between 27% and 83% in healthy volunteers.[13,14]

Two enzymes, xanthine oxidase and thiopurine methyl transferase (TPMT) create relatively inactive compounds whereas other enzymes are responsible for producing the cytotoxic and immunosuppressive thiopurine nucleotides. Inhibition of xanthine oxidase by drugs such as allopurinol can therefore greatly increase the therapeutic efficacy as well as the toxicity of azathioprine. The half-life of intracellular, active thiopurine nucleotides is estimated to be w1–2 weeks, and the concentrations do not vary over 24 h in patients receiving daily dosages.

Pashadika *et al.* investigated 145 patients (255 eyes) treated with azathioprine. The study showed that 62% of patients with active disease gained complete inactivity of inflammation, which sustained over at least 28 days within 1 year of therapy, and 47% of patients tapered systemic corticosteroids to <10 mg daily while maintaining control of inflammation within 1 year of therapy.[15]

A 2-year double-masked, placebo-controlled trial of azathioprine therapy in 73 Turkish male patients with Adamantiades–Behçet's disease found that azathioprine reduced the incidence of ocular involvement in patients initially free of ocular inflammation by more than 50%.[16]

Recommended dose: The use of azathioprine in ocular inflammatory disease is limited to low doses of 2–3 mg/kg/day orally.

Adverse effects: Common adverse effects are mostly gastrointestinal side effects such as nausea, vomiting, and diarrhea. Mild elevation of hepatic enzymes is also observed in less than 2% of patients. The most serious side effect is myelosuppression, which is common, dose-dependent, reversible, and varies highly among individual patients. Low-dose azathioprine therapy (1–2 mg/kg/d) resulted in leukopenia in 4.5% and thrombocytopenia in 2% of patients.[15] However, these patients were already suffering from chronic renal failure and had already received a renal transplant. Nevertheless, dose-related myelosuppresion is a serious adverse effect.

Monitoring: Complete blood counts and liver function tests should be monitored every 4–6 weeks.
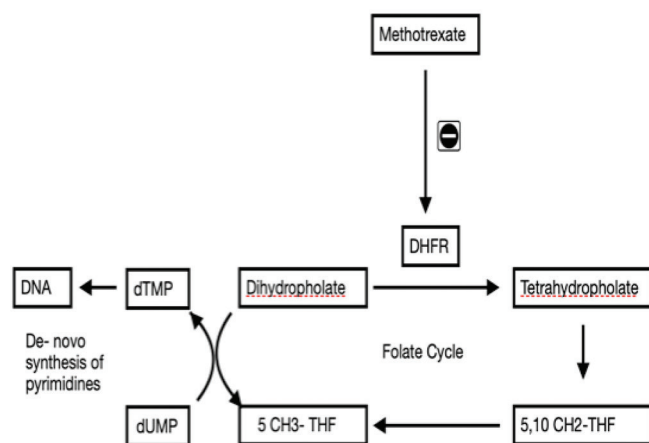

Figure 2: Metabolic pathway of mechanism of action of methotrexate. 5-CH$_3$-THF: 5-methyl-tetrahydrofolate; 5,10-CH$_2$-THF: 5,10-methylenetetrahydrofolate; DHFR: dihydrofolate reductase; dTMP: deoxythymidine monophosphate; dUMP: deoxyuridine monophosphate

Methotrexate

Methotrexate is a folic acid analog and an inhibitor of dihydrofolate reductase, the enzyme responsible for converting dihydrofolate to tetrahydrofolate. As such, methotrexate inhibits rapidly dividing cells, such as leukocytes, producing an anti-inflammatory effect [Fig. 2].

Methotrexate can be metabolized up to 35% in the intestinal flora when given orally. As the dose increases, the percentage of absorption decreases. Methotrexate is eliminated primarily through the kidney. The half-life of methotrexate is approximately 3 to 10 h, and at higher dosages, the half-life may be prolonged up to 15 h.

A series of 160 patients with chronic noninfectious uveitis published by Samson *et al.* were treated with methotrexate either as primary therapy or as a corticosteroid-sparing agent. A steroid-sparing response was achieved in 56% of patients, ocular inflammation was controlled in 76% of patients, and visual acuity improved or was maintained in 90% of patients.[17]

Recommended dose: A low dose of methotrexate therapy can usually be initiated as an oral dose of 7.5 mg once per week. The dose is often increased to 15 mg/week over weeks to months, depending on response. Doses greater than 20 mg/week are usually given subcutaneously or intramuscularly. Folic acid at 1–5 mg/day should be given concurrently to maintain adequate folate stores and to reduce toxicity.

Adverse effects: The more serious potential side effects include hepatotoxicity, bone marrow suppression, and interstitial pneumonia, which present as cough or dyspnea. Abnormal liver function tests occur in about 15% of patients, whereas only 0.3% of patients develop hepatic cirrhosis.[18]

Alopecia and rash may occur less commonly. Patients must also be counselled about the teratogenic potential of methotrexate and its contraindications in pregnancy. In addition, patients must abstain from alcohol consumption while taking methotrexate.

Monitoring: At the time of initiation of therapy, complete blood counts, hepatitis B surface antigen, and hepatitis C antibody should be done. Complete blood counts and liver function tests should be repeated every 1–2 months.

Mycophenolate Mofetil

Mycophenolate mofetil suppresses the immune system by selectively inhibiting the purine biosynthesis enzyme inosine monophosphate dehydrogenase (IMPDH), thereby depleting guanosine nucleotides that are essential for purine synthesis used in the proliferation of B and T lymphocytes.[19,20]

Galor *et al.* previously reported that scleritis and posterior uveitis/panuveitis were more likely to gain corticosteroid-sparing success with mycophenolate mofetil compared to other antimetabolite treatments.[21]

In 73 patients who received mycophenolate mofetil for ocular inflammation, corticosteroid-sparing success was achieved in 82% and 70% of patients at the <10 mg and the <5 mg prednisone thresholds, respectively, the majority within 6 months, and 40% were able to discontinue prednisone completely.[20]

Mycophenolate mofetil has high oral bioavailability and should be ingested on an empty stomach. Antacids reduce drug bioavailability by 15%.

Recommended dose: In uveitis, the suggested dose is 1 g twice daily taken orally.

Adverse effects: The most common side effects are gastrointestinal symptoms, including diarrhea, nausea, abdominal pain, and vomiting. Leukopenia, lymphocytopenia, and elevation of liver enzymes occurred infrequently.

Monitoring: Patients should be monitored with complete blood counts weekly for 4 weeks, then twice monthly for 2 months, thereafter monthly. Liver function tests need to be done every 3 months.

Alkylating agents

These agents act by alkylating DNA, leading to cross-linking of DNA, inhibition of DNA synthesis, and cell death. Alkylating agents induce remission but are not prescribed as first-line therapy due to toxicity.

Cyclophosphamide

Cyclophosphamide acts by exerting a cytotoxic effect on rapidly proliferating cells by alkylating nucleophilic groups on DNA bases, particularly the 7-nitrogen position of guanine, resulting in cross-linking, aberrant base pairing, ring cleavage, and depurination. It is cytotoxic to both resting and dividing lymphocytes. It suppresses both primary and established cellular and humoral immune responses, including delayed-type hypersensitivity. Cyclophosphamide was initially developed for cancer chemotherapy, was subsequently introduced in 1952 for the treatment of idiopathic uveitis, and has been used subsequently for various forms of ocular inflammation.[22]

Cyclophosphamide has been reported to be effective for the treatment of ocular manifestations of systemic autoimmune diseases, including Wegener's granulomatosis[23,24] rheumatoid vasculitis,[25] polyarteritis nodosa,[26] systemic lupus erythematosus,[27] and mucous membrane pemphigoid (MMP),[28] as well as for primary ocular inflammatory conditions including Mooren's ulcer, Behçet's disease,[29] and Vogt–Koyanagi–Harada syndrome.[30]

Cyclophosphamide gets extensively metabolized before excretion. Acrolein, one of its metabolites, is thought to be responsible for the urologic toxicity. 2-mercaptoethane sulfonate, a compound that binds acrolein, can be given to reduce bladder toxicity.

Recommended dose: Cyclophosphamide can be administered both orally (1–2 mg/kg daily) and intravenously (750–1000 mg/m² body surface area every 3 to 4 weeks). A consensus panel on immunosuppression for ocular disease concluded, based on previous available studies, that pulsed cyclophosphamide therapy for uveitis is less effective than oral cyclophosphamide.[8]

Adverse effects: The most common adverse event noted with cyclophosphamide is dose-dependent bone marrow suppression. Leukocyte counts of less than 2500–3500 cells/mL warrant discontinuation. Another serious complication is hemorrhagic cystitis (patients should be advised good intake of fluid to avoid) and increased risk of bladder cancer. Intermittent intravenous «pulse» cyclophosphamide is one of the approaches to avoid hemorrhagic cystitis.

It can cause ovarian suppression, testicular atrophy, azoospermia, alopecia, nausea, and vomiting. Other side effects are granulocytopenia, lymphopenia, and opportunistic infections.

Monitoring: CBC, urinalysis weekly initially and when dosing is stable, at least every 4 weeks

Chlorambucil

Chlorambucil is an alkylating agent that cross-links DNA by substituting an alkyl group for hydrogen ions in organic compounds, leading to faulty DNA replication, transcription, and nucleic acid function.

Recommended dose: In the treatment of uveitis, chlorambucil is typically given at a dose of 0.1–0.2 mg/kg/d as a single dose, which is continued for 1 year after disease quiescence. Tapering of corticosteroids may begin once the eye is quiet. Short-term high-dose therapy for 3–6 months also exists.[31-33]

A single dose of 6–12 mg/day can be given in these patients for 1 year.[31-33]

*Adverse effects***:** Bone marrow suppression, opportunistic infections, permanent sterility in men, and amenorrhea in women.

*Monitoring***:** Complete blood count initially weekly after that monthly.

T-Cell Inhibitors

T-cell inhibitors, as the name suggests, inhibit replication and activation of T-cell lymphocytes by inhibiting a phosphatase known as calcineurin, which dephosphorylates the nuclear factor of activated T-cells, which is a transcription factor regulating IL-2 production.

Cyclosporine

Cyclosporine preferentially affects immunocompetent T-lymphocytes, which are in the G0 and G1 phase of their cell cycle and leads to blocking replication. It reduces the ability of lymphocytes to produce lymphokines, such as IL-2.[34]

Cyclosporine A preferentially inhibits antigen-triggered signal transduction in T- lymphocytes, blunting the expression of many lymphokines, including IL-2 and antiapoptotic proteins. This pharmacologic action is mediated by the binding of cyclosporine to its immunophilin, cyclophilin, which inhibits the phosphatase calcineurin, thereby preventing the generation of the potent nuclear factor of activated T-cells. The drug is metabolized in the liver and excreted in the bile.

The efficacy of cyclosporine has been well-documented for Behçet's disease.[35] It has also been shown to be useful in the treatment of birdshot retinochoroidopathy, serpiginous choroiditis,[36] sympathetic ophthalmia, scleritis,[37] and panuveitis.

Recommended dose: 2.5–5.0 mg/kg/day (in 2 divided doses).

Adverse effects: Nephrotoxicity is the most serious adverse effect noted with cyclosporine, but it is more common at higher doses. It has been reported even for patients using lower dosages, leading to a recommendation that doses of 3 mg/kg/day or less to be used.[38] Cyclosporine can also cause hepatotoxicity, gingival hyperplasia, myalgia, tremors, paresthesia, hypomagnesemia, and hirsutism.

Monitoring: Blood pressure should be checked monthly for the initial 3 months and then every 3 months. Serum creatinine should be checked every 2 weeks initially and then monthly once the dosage has stabilized.

Table 3: Summary of all Immunosuppressant drugs

Drug	Dose	Common Uses	Adverse effects
Azathioprine	2-3 mg/kg/day	VKH, Sympathetic ophthalmia	Gastrointestinal upset Cytopenia Hepatitis
Methotrexate	15 mg/weekly	JIA Behcet's disease Sarcoidosis	Hepatitis Cytopenia
Mycophenolate mofetil	1 gm BID	JIA, Intermediate uveitis	Diarrhea Cytopenia
Cyclophosphamide	2 mg/kg/day	VKH, Wegener' s granulomatosis	Cytopenia Bladder toxicity
Chlorambucil	0.1 mg/kg/day	Adamantiades-Behcet's disease Sympathetic Ophthalmia	Cytopenia
Cyclosporine	2-5 mg/kg BID	Behcet's disease	Hypertension Nephrotoxicity Hirsutism
Tacrolimus	2-3 mg BID	Behcet's disease	Nephrotoxicity Neurotoxicity

Tacrolimus

Tacrolimus, also called FK506, is a macrolide antibiotic produced by *Streptomyces tsukubaensis*. Tacrolimus inhibits the activation of T lymphocytes by a mechanism similar to that of cyclosporine. Oral absorption of tacrolimus is poor and highly variable, ranging from 4%–93% (average: 25%). The drug is lipophilic, 99% of which becomes bound to serum proteins. Drug metabolism occurs via the cytochrome P-450 enzyme system in the liver and metabolites are excreted in the bile.[39]

As with cyclosporine, drugs that interfere with tacrolimus hepatic metabolism will result in increased serum concentrations. Impaired hepatic, but not renal function will affect the bioavailability. Absorption of tacrolimus from the gastrointestinal tract is both incomplete and variable, ranging from 4% to 93%.

A multicenter clinical trial in Japan examined the use of tacrolimus in 53 patients with noninfectious uveitis,[40] of whom had Behcet's disease.[40] The effectiveness was 38% in patients treated with an initial dosage of 0.05 mg/kg/day, 60% with 0.10 mg/kg/day, 83% with 0.15 mg/kg/day, and 79% with 0.20 mg/kg/day.

Recommended dose: Tacrolimus is available for both intravenous and oral administration. It is significantly more potent than cyclosporine and is given at initial oral doses of 0.05–0.15 mg/kg/day in uveitis patients.[39,40]

Adverse effects: Tacrolimus can cause renal impairment (28%), neurologic symptoms (21%), gastrointestinal symptoms (19%), hyperglycemia (13%), hypomagnesemia, tremor, headache, trouble sleeping, paresthesia, and hypertension.[40]

Monitoring: Blood pressure, weekly liver function tests; bilirubin; blood urea nitrogen; creatinine; electrolytes including calcium, magnesium, phosphate; cholesterol; and triglycerides levels also need to be monitored.

Tables 3 and 4 provide a summary of immunosuppressant drugs and their indications.

Recent Advances in Biologics and Selective Pharmacologic Agents for Uveitis and Ocular Inflammatory Diseases

The new group of medicines, the biological agents are therapeutic proteins designed to block the activity of

Table 4: Indications of Immunosuppressants[8]

Power of association	Diseases
Strong	Behcet disease Sympathetic ophthalmia Vogt-Koyanagi-Harada syndrome Rheumatoid necrotizing scleritis Wegener granulomatosis Relapsing polychondritis with scleritis Juvenile idiopathic arthritis
Relative	Intermediate uveitis Retinal vasculitis Severe chronic iridocyclitis
Questionable	Intermediate uveitis in children Sarcoid-associated uveitis not adequately responsive to steroid

biologically active molecules. These drugs belong to several different classes depending on their action such as Anti TNF agents, Anti IL 1 blockade, Anti IL6, Anti IL 17, B-cell blockers, and costimulatory blockade such as Abatacept. These are specifically targeted therapies with concomitant reduced side effects but come with certain risks such as unmasking of latent tuberculosis with anti- TNF agents and lack of vaccine response for 6–12 months with B-cell blockade.

Infliximab and **Adalimumab** are the two most commonly used biologics for noninfectious uveitis (NIU).[41]

Infliximab

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor-alpha (TNF-α) with both human and murine components. Infliximab is currently FDA-approved for the treatment of rheumatoid arthritis (RA), ulcerative colitis, Crohn's disease, psoriatic arthritis (PsA), plaque psoriasis, and ankylosing spondylitis.[41] Infliximab is used off-label for NIU.

Infliximab can be used as first-line therapy for selected systemic diseases such as Adamantiades–Behçet's disease[42-48] or in cases of moderate to severe idiopathic retinal vasculitis and optic disc inflammation, or as third-line therapy in uveitis refractory to corticosteroids and conventional IMT.

Infliximab is given intravenously at doses of 5, 7.5, 10, or 20 mg/kg[49-51] every 4 to 8 weeks with or without concomitant intravenous methylprednisolone at doses of 500 to 1000 mg for 1 to 3 days monthly. Doses can be tapered, and intervals are extended based on the clinical response. The mean number of infusions to show initial effectiveness is 2.05 and the mean number of infusions to achieve quiescence is 9.17 among patients with Vogt–Koyanagi–Harada (VKH), sarcoidosis, juvenile idiopathic arthritis (JIA), and idiopathic uveitis.[50] Initial anecdotal evidence suggests that the standard dose of infliximab (less than 10 mg/kg/dose) is less effective in the treatment of chronic uveitis.[50,51] One study showed the rapid efficacy of infliximab characterized by 96% resolution of acute inflammation 1 day after infusion.[52]

The half-life of infliximab is 10 days; however, its effects may persist for up to 2 months.[53] Because of its chimeric nature, infliximab is recommended to be administered concurrently with methotrexate or other immunomodulatory agents to decrease anti-chimeric antibody formation and increase the duration of drug efficacy.[54]

TNF-α inhibitors like infliximab are contraindicated in multiple sclerosis. Infections such as tuberculosis (TB), human immunodeficiency virus (HIV), syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), and toxoplasma must be ruled out before initiating therapy. Common side effects of TNF-α inhibitors include hypersensitivity while more severe side effects include serious infections, hematologic reactions, malignancies, and myocardial infarctions.

Patients on TNF-α inhibitors require regular blood evaluations including complete blood count, liver function tests, blood urea nitrogen, and serum creatinine levels every 6 to 12 weeks.

Adalimimab

Adalimumab is a fully-humanized monoclonal antibody against TNF-α, which binds soluble and transmembrane TNF-α. The United States Food and Drug Administration (FDA) approved adalimumab for the treatment of NIU after two successful phase 3 multicenter randomized controlled clinical trials, VISUAL I and II, demonstrated that time to treatment failure was significantly longer in the adalimumab group (>18 months) compared to the placebo group (8.3 months).[55,56]

Currently, adalimumab may be considered as first-line therapy for JIA-associated anterior uveitis or Adamantiades–Behçet's disease-related panuveitis.[57] Additional studies have supported the use of adalimumab in patients with Adamantiades–Behçet's disease-related panuveitis,[58,59] sarcoidosis-related uveitis, VKH syndrome, and birdshot chorioretinopathy (BSCR).[60,61,62,63]

Adalimumab is given subcutaneously with a loading dose of 80 mg followed by biweekly doses of 40 mg in adults and 20 to 40 mg in children, depending on body weight, every other week. Patients weighing ≥40 kg received 20 to 40 mg every other week, whereas patients weighing ≤40 kg received 10 to 20 mg every other week. The doses can escalate to weekly if needed[64] or be extended to every 3 weeks.[65] Such frequency was chosen due to a half-life of 15–19 days.[66] The rapid onset of response for uveitis was found after 2 to 16 weeks (mean 6 weeks) and was effective in 83% of children with severe JIA-associated uveitis.[65] Adalimumab can be used as monotherapy or in combination with systemic steroids or disease-modifying antirheumatic drugs (DMARDs), such as mycophenolate mofetil, azathioprine, methotrexate, or cyclosporin A.

TNF-α inhibitors such as adalimumab are contraindicated in multiple sclerosis. Infections such as tuberculosis (TB), human immunodeficiency virus (HIV), syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), and toxoplasma must be ruled out before initiating therapy. Common side effects of TNF-α inhibitors include hypersensitivity while more severe side effects include serious infections, hematologic reactions, malignancies, and myocardial infarctions.

Patients on TNF-α inhibitors require regular blood evaluations including complete blood count, liver function tests, blood urea nitrogen, and serum creatinine levels every 6 to 12 weeks.

Other biologic agents

Recent emerging and adopted therapies, including tocilizumab (STOP study),[67] sarilumab (SATURN study),[68] and **S**irolimus as a Therapeutic **A**pproach U**VE**itis (SAVE)-2 study (sirolimus),[69] have shown encouraging outcomes of these agents in the treatment of NIU with regard to minimizing corticosteroid dosage, reducing vitreous haze score (≥2 steps), and improving visual acuity with a relatively benign safety profile. However, other therapies such as secukizumab (INSURE study),[70] gevokizumab (EYEGUARD study),[71] ustekizumab (STELABEC study), apremilast,[74] and sotrastaurin[73] have shown no difference in the recurrence rate between placebo and treatment groups or lack of efficacy. Other promising therapies, including certolizumab,[74] canakinumab,[75] anakinra,[76] IFN-α,[77-79] abatacept,[80-85] filgotinib,[86] tofacitinib,[87] alemtuzumab,[88,89] and adrenocorticotropic hormone[90] have demonstrated efficacy in small case reports. Phase 2 clinical trials evaluating the safety and efficacy of filgotinib,[77] tofacitinib,[87] and adrenocorticotropic hormone[90] in NIU are currently ongoing.

At this point of time, a major restraint in the use of biological agents is the cost involved in using these agents [Table 5]. However, they have added a new dimension in treating refractory and recalcitrant noninfectious uveitis and are evolving as the first line treatments also in some uveitic entities.

Special Note: Immunosuppression in Pediatric age-group and Pregnancy

Immunosuppression In Pediatric Age Group

Noninfectious uveitis in children can be vision threatening with severe ocular morbidity. It is important to understand the role of immunosuppressive in pediatric uveitis. The systemic therapeutic options can be divided into systemic steroids (oral or intravenous), conventional synthetic disease-modifying agents (csDMARDs) such as methotrexate, antimetabolites, calcineurin inhibitors, alkylating agents, and finally biological DMARDs (bDMARDs).

In children, systemic steroids are a concern because prolonged use can cause delayed or reduced axial height and other side effects including weight gain, acne, insomnia, mood swings, glucose intolerance, osteoporosis, cataract, glaucoma, and psychiatric problems.[9,91,92] Steroids are generally used at doses of about 1 mg/kg/day, and up to 2 mg/kg/day for acute severe disease. They need to be tapered as quickly as possible and with the goal of less than 0.1 mg/kg per day, which is not likely to contribute to decreased or reduced growth.

Table 5: Average monthly cost of immunosuppressants drug prescription in India

Drug	Dose	Cost Rs/tab	Total monthly cost Rs
Azathioprine	50 mg/BD	Rs 10/50 mg tab	600
Methotrexate	15 mg/weekly	Rs 35/15 mg tab	140
MMF	1000 mg/BD	Rs 50/500 mg tab	6000
Cyclosporine	50 mg/BD	Rs 50/50 mg tab	3000
Tacrolimus	2-3 mg/OD	Rs 40/1 mg tab	2400
Cyclophosphamide	50 mg/BD	Rs 4/50 mg tab	240
Chlorambucil	5 mg/OD	Rs 200/5 mg tab	6000
Adalimumab	40 mg biweekly	Rs 25000/40 mg	50000
Etanercept	25 mg twice a week	Rs 6500/25 mg	68000
Infliximab	250 mg/8 weekly maintenance dose	Rs 42000/100 mg	52000

Methotrexate is a first-line steroid-sparing therapy in most pediatric uveitis. It can be given orally or subcutaneously. Subcutaneous administration provides better bioavailability, particularly at higher doses. The dosage can be per 0.5–1.0 mg/kg per week or 10–20 mg/m² with a maximum dose of 25 mg/wk. Methotrexate is effective in 60%–80% of the patients and takes 3 months to reach full efficacy.[18,93]

Other options include azathioprine, which besides being more cost-effective, works better in intermediate uveitis. The other antimetabolite that is used is mycophenolate, which is dosed at about 600 mg/m² given twice daily.[19] The toxicity includes gastrointestinal disturbances and leukopenia. Calcineurin inhibitors like cyclosporine are also used as a second-line therapy. They are metabolized at a higher rate in children, so the dosage is higher in children (up to 7 mg/kg).[37,38] These agents, however, require drug level monitoring as they can cause hirsutism, hypertension, and gum hypertrophy in addition to the well-described renal toxicity. The alkylating agents are less commonly used currently because of these side effects and the theoretical risk of malignancy.

The new group of medicines, the biological response modifiers, are used currently to achieve a therapeutic response when the csDMARDs are ineffective.

Adalimumab, a fully-humanized monoclonal antibody against TNF has been tried in pediatric uveitis and approved by various regulatory authorities. The first phase 3 trials to demonstrate the role of adalimumab in uveitis is the VISUAL studies published in the *New England Journal of Medicine* and the *Lancet* in 2016, which showed the response in patients with inflammation not fully controlled with anti-metabolites.[55,57] The dosage in children is 20 mg every 2 weeks in children less than 30 kg, as seen in the SYCAMORE trial.[94] Other trials show that the dose can be escalated to once a week in refractory cases and has been shown to be beneficial.

The other biologics that have been used is infliximab, which is a chimeric monoclonal antibody against TNF alpha. It is used as an IV infusion with the loading dose of 3–10 mg/kg/day in children and is given as a monthly dose.[95] In India, because of the risk of tuberculosis, generally 5 mg/kg is used.

Other TNF blockers such as golimumab and certolizumab have been used and have shown efficacy in children. IL-6 inhibitors like tocilizumab have been used and have been found to be beneficial in patients with macular edema. B-cell inhibitors such as rituximab have been tried in resistant pediatric uveitis;

they generally take about 3–5 months to act and retreatment is required at 6 to 12 months.[95]

Other biologics such as abatacept have been employed in a small series as shown by the European multinational interdisciplinary working group for uveitis in childhood. More drugs are in the pipeline. Early aggressive therapy has been shown to improve ocular and visual outcomes and is associated with reduced risk of complications and improved control of inflammation within 3 years. It is important to remember that oral steroids may be an option for adults, but steroids should not be used in children for more than 3 months at a time.[96]

There is no consensus on the optimum time to initiate antimetabolites or biologic agents, but experience shows that the aim of treatment should be to make the child steroid-free by 3 months (i.e. avoid oral or topical steroid drops). Some studies show that up to two drops of steroids have been shown to limit complications such as cataract and glaucoma.[96]

Controversy exists about the length of therapy for both csDMARDs and bDMARDs and the correct tapering schedule. The majority of studies suggest that a minimum of 2–3 years of steroid-free remission of uveitis should precede any attempts to reduce the dose of immunosuppression.

Megan Cann *et al.* have published outcomes of noninfectious pediatric uveitis in the era of biological therapy, which shows that approximately 30% of the patients of pediatric uveitis will require the use of biologicals.[95] It has been shown that the use of systemic immunosuppression has resulted in fewer ocular surgeries in pediatric noninfectious uveitis.[96]

Within the Indian context, the cost of TNF inhibitors is prohibitive. Other options include using two DMARDS like methotrexate and mycophenolate. The challenge managing a child with noninfectious uveitis can be a daunting one. For best visual outcomes, it is very important that the child be evaluated and managed by pediatric uveitis and pediatric rheumatology teams who can coordinate and offer the child the proper choice of csDMARD or bDMARD depending upon the disease activity and complications of uveitis and/or systemic disease.

Immunosuppression in pregnancy

Pregnancy presents another challenge in the management of uveitis. It is important to understand that pregnancy and immunosuppression create issues regarding fetal well-being in which the fetus can have fetal abnormalities or prematurity-related issues. During the first trimester in

pregnancy, uveitis can flare up while in the second and third semester, the inflammation can reduce on its own because of the increase in intrinsic hormones. The commonly used drugs including oral steroids, IMT agents such as methotrexate and mycophenolate, and TNF inhibitors such as adalimumab and infliximab, may affect pregnancy, especially methotrexate. Since we do not have randomized control trials due to ethical issues, retrospective case studies and animal studies guide us in the management of the use of these drugs.

It is important that all patients on immunosuppressants are advised regarding family planning. The various drugs, which are advised not to be taken when planning a pregnancy are methotrexate, mycophenolate, cyclophosphamide, and leflunomide.[97] The drugs, which have been shown to be safe in pregnancy are steroids (low dose) hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, and TNF blockers like infliximab, adalimumab, and certolizumab. There is, however, a placental transfer of these drugs. Infliximab can be limited to the first trimester, adalimumab to the second trimester, and certolizumab to the third trimester since it has a low placental transfer.[98-100] Children whose mothers have been exposed to TNF blockers should not be given live-attenuated vaccines until 7 months of age. Other biologicals like rituximab and tocilizumab have limited data so they should be avoided in pregnancy. Various drugs such as methotrexate, mycophenolate, and cyclophosphamide should be avoided in both men and women at least 3–6 months before planning a pregnancy.[97]

It is important that rheumatologists and obstetricians discuss with patients the risk of the disease and the risk to the fetus. It is also important to have a detailed ultrasound between 12 and 16 weeks of pregnancy. In isolated uniocular disease, it is possible to use periocular/intraocular steroids, which reduces the side effect of the drugs. To conclude, it is important to understand that pregnancy in uveitis is a challenging situation for uveitis specialists.[98-100]

Conclusion

Corticosteroids are the mainstay of treatment in patients with ocular inflammation. However, long-term use of corticosteroids is associated with significant adverse effects. The addition of immunosuppressive agents helps in achieving a steroid-sparing effect and long-term remission. However, immunosuppressive agents also have their own potential adverse effects that ophthalmologists, including uveitis specialists, need to be aware of. In a tuberculosis-endemic country such as India, immunosuppressive therapy needs to be used with significant caution. The use of these agents also requires close monitoring and individualized dosing. Biological agents are limited in their use at this point of time because of the costs involved. If used properly, the introduction of immunomodulatory medications may lead to safe and long-term suppression of ocular inflammation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Jabs DA, Busingye J. Approach to the diagnosis of the Uveitides. Am J Ophthalmol 2013;156:228-36.
2. Nussenblatt RB. The natural history of uveitis. Int Ophthalmol 1990;14:303-8.
3. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.
4. Zagora SL, Symes R, Yeung A, Yates W, Wakefield D, McCluskey PJ. Etiology and clinical features of ocular inflammatory diseases in a tertiary referral centre in Sydney, Australia. Ocul Immunol Inflamm 2016;30:1-8.
5. Agrawal R, Agarwal A, Jabs DA, Kee A, Testi I, Mahajan S, et al. Standardization of nomenclature for ocular tuberculosis-Results of collaborative ocular tuberculosis study (COTS) workshop. Ocul Immunol Inflamm 2019:1-11. doi: 10.1080/09273948.2019.1653933.
6. Gordon D, McLean J. Effects of pituitary adrenocortico tropic hormone (ACTH) therapy in ophthalmologic conditions. J Am Med Assoc 1950;142:1271-6.
7. Durrani K, Zakka FR, Ahmed M, Memon M, Siddique SS, Foster CS. Systemic therapy with conventional and novel immunomodulatory agents for ocular inflammatory disease. Surv Ophthalmol 2011;56:474-510.
8. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: Recommendations of an expert panel. Am J Ophthalmol 2000;130:492-513.
9. Roda Perez E. Case of uveitis of unknown etiology treated with nitrogen mustards. Rev Clin Esp 1951;41:265-7.
10. Agarwal M, Zierhut M. Corticosteroids. In: Zierhut M, Pavesio C, Ohno S, Oréfice F, Rao NA, editors. Intraocular inflammation. Springer-Verlag Berlin Heidelberg; 2016. p. 273.
11. Kok C, Sambrook PN. Secondary osteoporosis in patients with an osteoporotic fracture. Best Pract Res Clin Rheumatol 2009;23:769-79.
12. Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocortidoid usage in the United States: A general population perspective. Arthr Care Res 2013;65:294-8.
13. Elion GB, Hitchings JH. Azathioprine. In: Handbook of Experimental Pharmacology. vol. 38. 1975. p. 404-25.
14. Chan GL, Erdmann GR, Gruber SA, Matas AJ, Canafax DM. Azathioprine metabolism: Pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. J Clin Pharmacol 1990;30:358-63.
15. Pashadika S, Kempen JH, Newcomb CW, Liesegang TL, Pujari SS, Rosenbaum JT, et al. Azathioprine for ocular inflammatory diseases. Am J Ophthalmol 2009;148:500-9.e2.
16. Yazici H, Pazarli H, Barnes CG, Tüzün Y, Ozyazgan Y, Silman A, et al. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990;322:281-5.
17. Samson CM, Waheed N, Baltatzis S, Foster CS. Methotrexate therapy for chronic noninfectious uveitis: Analysis of a case series of 160 patients. Ophthalmology 2001;108:1134-9.
18. Kremer JM, Alarcon GS, Lightfoot RW Jr, Willkens RF, Furst DE, Williams HJ, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994;37:316-28.
19. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology 2005;112:1472-7.
20. Daniele E, Thorne JE, Craig W, Newcomb CW, Pujari SS, Kaçmaz RO, et al. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol 2010;149:423-32.
21. Galor A, Jabs DA, Leder HA, Kedhar SR, Dunn JP, Peters GB 3rd, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology 2008;115:1826-32.
22. Roda Perez E. Nitrogen mustard therapy of uveitis of unknown etiology [undetermined language]. Rev Clin Esp 1952;44:173-80.

23. Biswas J, Babu K, Gopal L, Krishanakumar S, Suresh S, Ramakrishnan S. Ocular manifestations of Wegener's granulomatosis: Analysis of nine cases. Indian J Ophthalmol 2003;51:217-23.

24. Charles SJ, Meyer PA, Watson PG. Diagnosis and management of systemic Wegener's granulomatosis presenting with anterior ocular inflammatory disease. Br J Ophthalmol 1991;75:201-7.

25. Jackson CG, Williams HJ. Disease-modifying antirheumatic drugs: Using their clinical pharmacological effects as a guide to their selection. Drugs 1998;56:337-44.

26. Colmegna I, Maldonado-Cocco JA. Polyarteritis nodosa revisited. Curr Rheumatol Rep 2005;7:288-96.

27. Sibilia J. Treatment of systemic lupus erythematosus in 2006. Joint Bone Spine 2006;73:591-8.

28. Saw VP, Dart JK, Rauz S, Ramsay A, Bunce C, Xing W, *et al.* Immunosuppressive therapy for ocular mucous membrane pemphigoid: Strategies and outcomes. Ophthalmology 2008;115:253-61.

29. Kazokoglu H, Saatci O, Cuhadaroglu H, Eldem B. Long-term effects of cyclophosphamide and colchicine treatment in Behcet's disease. Ann Ophthalmol 1991;23:148-51.

30. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 1995;39:265-92.

31. Tabbara KF. Chlorambucil in Behcet's disease. Ophthalmology 1983;90:906-8.

32. Andrasch RH, Pirofsky B, Burns RP. Immunosuppressive therapy for severe chronic uveitis. Arch Ophthalmol 1978;96:247-51.

33. 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;109:137-42.

34. Gerber DA, Bonham CA, Thomson AW. Immunosuppressive agents: Recent developments in molecular action and clinical application. Transplant Proc 1998;30:1573-9.

35. 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;1:1093-6.

36. Akpek EK, Baltatzis S, Yang J, Foster CS. Long-term immunosuppressive treatment of serpiginous choroiditis. Ocul Immunol Inflamm 2001;9:153-67.

37. McCarthy JM, Dubord PJ, Chalmers A, Kassen BO, Rangno KK. Cyclosporine A for the treatment of necrotizing scleritis and corneal melting in patients with rheumatoid arthritis. J Rheumatol 1992;19:1358-61.

38. Isnard Bagnis C, Tezenas du Montcel S, Beaufils H, Jouanneau C, Chantal Jaudon, M, Maksud P, *et al.* Long-term renal effects of low-dose cyclosporine in uveitis-treated patients: Follow-up study. J Am Soc Nephrol 2002;13:2962-8.

39. Mochizuki M, Masuda K, Sakane T, Ito K, Kogure M, Sugino N, *et al.* A clinical trial of FK506 in refractory uveitis. Am J Ophthalmol 1993;115:763-9.

40. Ishioka M, Ohno S, Nakamura S, Isobe K, Watanabe N, Ishigatsubo Y, *et al.* FK506 treatment of noninfectious uveitis. Am J Ophthalmol 1994;118:723-9.

41. Thomas AS. Biologics for the treatment of noninfectious uveitis: Current concepts and emerging therapeutics. Curr Opin Ophthalmol 2019;30:138-50.

42. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, *et al.* 2018 update of the EULAR recommendations for the management of Behcet's syndrome. Ann Rheum Dis 2018;77:808-18.

43. Markomichelakis N, Delicha E, Masselos S, Fragiadaki K, Kaklamanis P, Sfikakis PP. A single infliximab infusion vs corticosteroids for acute panuveitis attacks in Behcet's disease: A comparative 4-week study. Rheumatology (Oxford, England) 2011;50:593-7.

44. 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;127:819-22.

45. Markomichelakis N, Delicha E, Masselos S, Sfikakis PP. Intravitreal infliximab for sight-threatening relapsing uveitis in Behcet disease: A pilot study in 15 patients. Am J Ophthalmol 2012;154:534-41.e1.

46. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behcet's disease. Lancet (London, England) 2001;358:295-6.

47. 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;31:1362-8.

48. Okada AA, Goto H, Ohno S, Mochizuki M. Multicenter study of infliximab for refractory uveoretinitis in Behcet disease. Arch Ophthalmol 2012;130:592-8.

49. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmol 2006;113:308-14.

50. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmol 2006;113:860-4.e2.

51. Sukumaran S, Marzan K, Shaham B, Reiff A. High dose infliximab in the treatment of refractory uveitis: Does dose matter? ISRN Rheumatol 2012;2012:765380.

52. Sfikakis PP, Kaklamanis PH, Elezoglou A, Katsilambros N, Theodossiadis PG, Papaefthimiou U, *et al.* Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behcet disease. Ann Intern Med 2004;140:404-6.

53. Nestorov I. Clinical pharmacokinetics of TNF antagonists: How do they differ? Semin Arthritis Rheum 2005;34:12-8.

54. Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol 2000;27:841-50.

55. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, *et al.* Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): A multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet (London, England) 2016;388:1183-92.

56. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, *et al.* Adalimumab in patients with active noninfectious uveitis. N Engl J Med 2016;375:932-43.

57. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmol 2014;121:785-96.e3.

58. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behçet's disease. Eye 2007;21:824-5.

59. Bawazeer A, Raffa LH, Nizamuddin SH. Clinical experience with adalimumab in the treatment of ocular Behcet disease. Ocular Immunol Inflamm 2010;18:226-32.

60. Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA, *et al.* Adalimumab therapy for refractory uveitis: Results of a multicentre, open-label, prospective trial. Br J Ophthalmol 2013;97:481-6.

61. Diaz-Llopis M, Salom D, Garcia-de-Vicuna C, Cordero-Coma M, Ortega G, Ortego N, *et al.* Treatment of refractory uveitis with adalimumab: A prospective multicenter study of 131 patients. Ophthalmol 2012;119:1575-81.

62. Fabiani C, Vitale A, Emmi G, Bitossi A, Lopalco G, Sota J, *et al.* Long-term retention rates of adalimumab and infliximab in non-infectious intermediate, posterior, and panuveitis. Clin Rheumatol 2019;38:63-70.

63. Fabiani C, Vitale A, Rigante D, Emmi G, Bitossi A, Lopalco G, *et al.* Comparative efficacy between adalimumab and infliximab in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis: A retrospective observational study of 107 patients. Clin Rheumatol 2019;38:407-15.

64. Dubinsky MC, Rosh J, Faubion WA Jr., Kierkus J, Ruemmele F, Hyams JS, *et al.* Efficacy and safety of escalation of Adalimumab therapy to weekly dosing in pediatric patients with Crohn's disease. Inflamm Bowel Dis 2016;22:886-93.

65. 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;91:319-24.

66. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, *et al.* Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: A pilot study. Clin Ther 2003;25:1700-21.

67. Sepah YJ, Sadiq MA, Chu DS, Dacey M, Gallemore R, Dayani P, *et al.* Primary (Month-6) outcomes of the STOP-uveitis study: Evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. Am J Ophthalmol 2017;183:71-80.

68. Heissigerova J, Callanan D, de Smet MD, Srivastava SK, Karkanova M, Garcia-Garcia O, *et al.* Efficacy and safety of Sarilumab for the treatment of posterior segment noninfectious uveitis (SARIL-NIU): The Phase 2 SATURN study. Ophthalmol 2019;126:428-37.

69. Ibrahim MA, Sepah YJ, Watters A, Bittencourt M, Vigil EM, Do DV, *et al.* One-year outcomes of the SAVE study: Sirolimus as a therapeutic approach for uveitis. Transl Vision Sci Technol 2015;4:4.

70. Dick AD, Tugal-Tutkun I, Foster S, Zierhut M, Melissa Liew SH, Bezlyak V, *et al.* Secukinumab in the treatment of noninfectious uveitis: Results of three randomized, controlled clinical trials. Ophthalmol 2013;120:777-87.

71. Tugal-Tutkun I, Pavesio C, De Cordoue A, Bernard-Poenaru O, Gul A. Use of Gevokizumab in patients with Behcet's disease uveitis: An international, randomized, double-masked, placebo-controlled study and open-label extension study. Ocular Immunol Inflamm 2018;26:1023-33.

72. Apremilast in the Treatment of Uveitis NCT00889421.

73. Safety, Tolerability, and Efficacy of AEB071 in the Treatment of Uveitis NCT00615693.

74. Yamaguchi K, Hayashi T, Takahashi G, Momose M, Asahina A, Nakano T. Successful Certolizumab Pegol treatment of chronic anterior uveitis associated with psoriasis vulgaris. Case Rep Ophthalmol 2018;9:499-503.

75. Simonini G, Xu Z, Caputo R, De Libero C, Pagnini I, Pascual V, *et al.* Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. Arthritis Rheum 2013;65:513-8.

76. Teoh SCB, Sharma S, Hogan A, Lee R, Ramanan AV, Dick AD. Tailoring biological treatment: Anakinra treatment of posterior uveitis associated with the CINCA syndrome. Br J Ophthalmol 2007;91:263-4.

77. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong DLT, *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;91:335-9.

78. Sobaci G, Bayraktar Z, Bayer A. Interferon alpha-2a treatment for serpiginous choroiditis. Ocular Immunol Inflamm 2005;13:59-66.

79. Deuter CM, Gelisken F, Stubiger N, Zierhut M, Doycheva D. Successful treatment of chronic pseudophakic macular edema (Irvine-Gass syndrome) with interferon alpha: A report of three cases. Ocular Immunol Inflamm 2011;19:216-8.

80. Birolo C, Zannin ME, Arsenyeva S, Cimaz R, Miserocchi E, Dubko M, *et al.* comparable efficacy of Abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. J Rheumatol 2016;43:2068-73.

81. Tappeiner C, Miserocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, *et al.* Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2015;42:706-11.

82. Zulian F, Balzarin M, Falcini F, Martini G, Alessio M, Cimaz R, *et al.* Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. Arthritis Care Res 2010;62:821-5.

83. Angeles-Han S, Flynn T, Lehman T. Abatacept for refractory juvenile idiopathic arthritis-associated uveitis: A case report. J Rheumatol 2008;35:1897-8.

84. Kenawy N, Cleary G, Mewar D, Beare N, Chandna A, Pearce I. Abatacept: A potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis. Graefe Arch Clin Exp Ophthalmol 2011;249:297-300.

85. Marrani E, Paganelli V, de Libero C, Cimaz R, Simonini G. Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: A case series. Graefe Arch Clin Exp Ophthalmol 2015;253:1813-6.

86. A Phase 2, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Filgotinib in Subjects with Active NIU (NCT03207815).

87. Tofacitinib for Inflammatory Eye Disease NCT03580343.

88. Willis MD, Pickersgill TP, Robertson NP, Lee RWJ, Dick AD, Carreno E. Alemtuzumab-induced remission of multiple sclerosis-associated uveitis. Int Ophthalmol 2017;37:1229-33.

89. Dick AD, Meyer P, James T, Forrester JV, Hale G, Waldmann H, *et al.* Campath-1H therapy in refractory ocular inflammatory disease. Br J Ophthalmol 2000;84:107-9.

90. Agarwal A, Hassan M, Sepah YJ, Do DV, Nguyen QD. Subcutaneous repository corticotropin gel for non-infectious panuveitis: Reappraisal of an old pharmacologic agent. Am J Ophthalmol Case Rep 2016;4:78-82.

91. Miraldi Utz V, Bulas S, Lopper S, Fenchel M, Sa T, Mehta M, *et al.* Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. Pediatr Rheumatol Online J 2019;17:79.

92. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Exp Ophthalmol 2005;33:461-8.

93. 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;11:131-9.

94. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, *et al.* Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med 2017;376:1637-46.

95. Cann M, Ramanan AV, Crawford A, Dick AD, Clarke SLN, Rashed F, *et al.* Outcomes of non-infectious Paediatric uveitis in the era of biologic therapy. Pediatr Rheumatol 2018;16:51.

96. Cheung CSY, Mireskandari K, Ali A, Silverman E, Tehrani N. Earlier use of systemic immunosuppression is associated with fewer ophthalmic surgeries in paediatric non-infectious uveitis. Br J Ophthalmol 2019. doi: 10.1136/bjophthalmol-2019-314875.

97. Ponticelli C, Moroni G. Fetal toxicity of immunosuppressive drugs in pregnancy. J Clin Med 2018;7:552.

98. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, *et al.* The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795-810.

99. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, *et al.* BSR and BHPR standards, guidelines and audit working group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: Standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016;55:1693-7.

100. Puchner A, Gröchenig HP, Sautner J, Helmy-Bader Y, Juch H, Reinisch S, *et al.* Immunosuppressives and biologics during pregnancy and lactation: A consensus report issued by the Austrian Societies of Gastroenterology and Hepatology and Rheumatology and Rehabilitation. Wien Klin Wochenschr 2019;131:29-44.