

Medical Management of Uveitis – Current Trends

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Uveitis is a challenging disease to treat. Corticosteroids have been used in the treatment of uveitis for many years. Immunosuppressives are gaining momentum in recent years in the treatment of uveitis. In this article we present an overview of current treatment of uveitis and the major breakthroughs and advances in drugs and ocular drug delivery systems in the treatment of uveitis.

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Uveitis is a potentially sight threatening disease. It may occur due to an infection or may be due to an autoimmune etiology. Specific antimicrobial therapies with or without corticosteroids are used in cases of infectious uveitis. Several drugs are available for the management of noninfectious uveitis including corticosteroids, immunosuppressive agents, and more recently biologics. The treatment of uveitis is evolving with newer drugs and innovative advances in ocular drug delivery. This is due to better understanding of the pathophysiology of disease and barriers in drug delivery. In this article, we present an overview of current treatment of uveitis and the major breakthroughs and advances in drugs and ocular drug delivery systems in the treatment of uveitis. The following sections will be discussed in detail in the manuscript:

- I. Corticosteroids:
 - A. Local delivery of corticosteroids:
 1. Topical corticosteroids
 2. Iontophoresis
 3. Periocular injections
 4. Intravitreal injections and inserts
 - B. Systemic oral steroids (oral and intravenous)
- II. Immunosuppressants
- III. Biologics
- IV. Adjuvant therapy:
 - A. Cycloplegics
 - B. Newer nonsteroidal anti-inflammatory agents
 - C. Anti-vascular endothelial growth factor (anti-VEGF) therapy
- V. Current concepts in infectious uveitis management

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Corticosteroids are the first line of therapy in patients with noninfectious ocular inflammatory diseases as these drugs are inexpensive, potent, and act fast. They may be administered either topically, periocular injections, or systemically (oral, intramuscular or intravenous routes). The mechanism of action of corticosteroids is complex and incompletely understood. They act at the cellular and molecular level.^[1,2]

Topical Corticosteroids

Topical corticosteroids are used in the treatment of anterior uveitis. Concentrations of these steroids in the aqueous, depends on the rate of their diffusion across the cornea.^[2,3] Among the topical corticosteroids, prednisolone acetate eye drops provides greater theoretical anti-inflammatory effect than either dexamethasone or betamethasone. This is due to two reasons: Firstly, the concentration of betamethasone and dexamethasone eye preparations is 0.1% as compared to 1% for prednisolone acetate and secondly, though prednisolone acetate is six times less potent on a molar basis than betamethasone or dexamethasone, the penetration into the cornea of prednisolone acetate is much more than betamethasone or dexamethasone. Dosing frequency and the length of time the medication stays in contact with ocular surface also influences efficacy. Suspensions have a higher degree of anti-inflammatory effect.^[2,3]

Other corticosteroid eye preparations include fluorometholone, rimexolone, and loteprednol etabonate. These are called “soft steroids” due to the lesser propensity of increasing the intraocular pressure (IOP)^[2,4,5] Another recently approved steroid is difluprednate (0.05%) (difluoroprednisolone butyrate acetate). It is a synthetic fluorinated prednisolone derivative. This has greater glucocorticosteroid receptor binding activity than prednisolone acetate. This is due to fluorination at C6 and C9 positions and replacement of C-17 hydroxyl group with butyrate ester, which increases its specificity for the glucocorticoid receptor. Greater corneal penetration is achieved by the addition of acetate ester at position C-21. Stringer *et al.*, have reported that consistent dose uniformity is achieved with

difluprednate ophthalmic emulsion 0.05% when compared with branded and generic prednisolone acetate ophthalmic suspensions 1%.^[6] Foster *et al.*, have inferred from their studies that a qid dosing of difluprednate ophthalmic emulsion 0.05% is as effective as eight times dosing with prednisolone acetate 1% ophthalmic suspension in the treatment of endogenous anterior uveitis.^[7] Reports on its use in post cataract surgery show potency equivalent to prednisolone acetate.^[8,9] Elevation of IOP in patients with uveitis especially in children treated with topical difluprednate have been reported in the literature. One needs to exert caution while using this preparation in children.^[10,11] Table 1 outlines the list of commonly available topical corticosteroid preparations.^[2]

Side effects of topical administration of steroids: Elevation of IOP, susceptibility to infections, impaired corneal or scleral wound healing, corneal epithelial toxicity, and crystalline keratopathy are reported with the use of topical administration of corticosteroids.

It is important that patients on topical corticosteroids be regularly monitored to assess the response to therapy as well as development of side effects.

Iontophoresis

Iontophoresis is a noninvasive method of application of low current to an ionizable substance (drug) to increase its mobility across a surface by electrochemical repulsion. Phase 2 trials have been conducted on delivery of dexamethasone phosphate by ocular iontophoresis in noninfectious anterior uveitis. Dexamethasone phosphate (40 mg/ml, EGP-437) is a prodrug and is a good candidate for iontophoresis delivery, as it possesses two acidic protons (pK values of 1.9 and 6.4), making it highly water-soluble formulation with a high buffering capacity. In addition, it has a well-characterized safety and efficacy profiles for ophthalmic use. To deliver dexamethasone phosphate, which is an anion at physiologic pH, a cathodic delivery is used to produce hydroxide ions, which drive the dexamethasone phosphate anions into the ocular tissues, by electrochemical repulsion. Also, these hydroxyl ions (OH) increase the pH of the drug solution, shifting the equilibrium

Table 1: Commonly available topical corticosteroid preparations

Medication	Concentration (%)	Formulation
Dexamethasone sodium phosphate	0.1	Solution
Dexamethasone alcohol	0.1	Suspension
Fluorometholone acetate	0.1	Suspension
Fluorometholone alcohol	0.1–0.125	Suspension
Loteprednol	0.2–0.5	Suspension
Betamethasone phosphate	0.1–0.5	Solution
Prednisolone acetate (LS)	0.12–0.125	Suspension
Prednisolone acetate	1	Suspension
Prednisolone sodium phosphate	0.125–1	Solution
Difluprednate	0.05	Emulsion
Rimexolone	1	Suspension

towards ionized state, and hence increasing the efficiency while buffering the formulation.

The Eye Gate II Delivery System (EGDS, Eye gate Pharmaceuticals, Inc., Waltham, MA) is a novel ocular iontophoresis system designed to deliver substantial levels of drug noninvasively into the anterior segments of the eye while minimizing systemic distribution.

In this trial, 40 eyes were randomly assigned, to receive one of the four iontophoresis dose levels of EGP-437 for duration of 4 min (1.6 mA-min at 0.4 mA; 4.8 mA-min at 1.2 mA; 10 mA-min at 2.5 mA; and 14 mA-min at 3.5 mA). The results show effectivity and fewer adverse events at lower doses (1.6 mA-min group).^[12]

Periocular Steroids

They are indicated in moderate to severe chronic or recurrent uveitis, cystoid macular edema, and in cases with anterior chamber inflammation not responding adequately to topical corticosteroids. Periocular steroids offer the benefit of higher, local, and sustained drug to the eye with greater posterior segment penetration. Posterior injections are typically given via the posterior subtenon approach using the Smith and Nozik technique.^[1,2,13,14] Orbital floor injections provide an alternative to posterior subtenon injection. Anterior injections are often given subconjunctivally on the inferior or superior bulbar surface. Table 2 outlines the list of injectable corticosteroid preparations.

The duration of action differs for various injectable corticosteroid preparations.

Side effects of periocular steroids: Periocular administration may cause a variety of side effects, which include increased IOP and glaucoma, ptosis, cataract, and inadvertent globe perforation.^[2,3]

Intravitreal Steroids

Intravitreal corticosteroids, such as triamcinolone acetonide are often used to manage noninfectious intermediate and posterior uveitis and its complications such as cystoid macular edema due to the direct action and hence greater efficacy. It is administered as 4 mg in 0.1 ml. The effects are usually short-lived and may last for 6–8 weeks.^[15] Sustained release corticosteroid intraocular implants may be considered in place of repeated injections. Retisert^[16] (Bausch and Lomb, Rochester, NY) contains fluocinolone acetonide 0.59 mg (requires a

Table 2: Injectable corticosteroid preparations

Medication	Concentration	Approximate duration of action
Dexamethasone sodium phosphate	4, 10, and 24 mg/ml, solution	1–2 days
Triamcinolone acetonide	40 mg/ml, suspension	2–4 months intraocular; <3 months periocular
Betamethasone phosphate	3 mg/ml, solution	1–2 days
Betamethasone acetate/phosphate	3.6 mg/ml, suspension	7–10 days

surgical procedure to suture the implant to the scleral wall) that achieves sustained release of approximately 2.5 years. Another implant for treatment of noninfectious posterior uveitis is a dexamethasone intravitreal implant^[17] (Ozurdex, Allergan, Inc., Irvine, CA). It is a 0.7 mg biodegradable implant that delivers a sustained release of dexamethasone over 3–6 months through the Novadur solid polymer delivery system, which is given intravitreally via an injector.

Serious side effects include cataract, increased IOP, glaucoma, retinal detachment, vitreous hemorrhage, and endophthalmitis.

Systemic Steroids

Systemic corticosteroids play an important role in the management of intraocular inflammation.^[18] Indications include inflammation; which is moderate to severe, bilateral, beyond anterior segment, resistant to local therapy, or associated with systemic disease. Cortisone, hydrocortisone, prednisone, and fludrocortisone are the different steroids available for oral administration. Prednisone is the most common corticosteroid used orally in the treatment of uveitis. The initiation of therapy is typically 0.5–1 mg/kg daily followed by a slow taper once the inflammation is under control.^[3] Optimally, the dose should be less than 0.1 mg/kg daily within 3 months of initiating therapy. For immediate control of vision threatening diseases (necrotizing scleritis, bilateral serous detachments), methyl prednisolone sodium succinate can be given intravenously over a period of more than 30 min. The usual regimen consists of 250–1,000 mg/day (pulse dose) intravenously on 3 consecutive days.^[3] Table 3 outlines the guidelines for tapering and monitoring while on systemic corticosteroids. Systemic corticosteroids can cause a variety of systemic side effects. Table 4 outlines the adverse effects of systemic corticosteroids.

Table 3: Suggested guidelines for the use of prednisone for chronic ocular inflammation⁴

Parameter	Suggested guidelines
Initial dose	1 mg/kg/day
Maximum adult oral dose	60–80 mg/day
Maintenance dose (adult)	£10 mg/day
Tapering schedule	<ul style="list-style-type: none"> • Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks • 40–20 mg/day, decrease by 5 mg/day every 1–2 weeks • 20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks • 10–0 mg/day, decrease by 1–2.5 mg/day every 1–4 weeks
Monitor	<ul style="list-style-type: none"> • Blood pressure, weight, glucose every 3 months • Lipids (cholesterol and triglycerides) annually • Bone density within first 3 months and annually thereafter
Supplemental therapy	<ul style="list-style-type: none"> • Calcium 1,500 mg daily and vitamin D 800 IU daily • Estrogens and antiresorptive agents as needed

Immunosuppressive Agents

Immunosuppressive drugs can be classified as antimetabolites, T cell inhibitors, and alkylating agents.^[4] The antimetabolites include methotrexate, azathioprine, and mycophenolate mofetil.^[4,18] The T cell inhibitors include cyclosporine, tacrolimus, voclosporin,^[19] and sirolimus.^[20,21] The alkylating agents include cyclophosphamide and chlorambucil.^[4]

The mechanism of action, required dosage, and side effects of various immunosuppressives are listed in Table 5. These drugs take many weeks to have an effect, so initial therapy of ocular inflammation typically include high dose of systemic steroids. Immunosuppressive therapy can be started simultaneously with corticosteroids in severe cases or during the tapering of oral corticosteroids 4–8 weeks later in cases of chronic uveitis.

Tuberculosis and HIV needs to be ruled out prior to starting immunosuppressive therapy. Complete blood counts and platelet count need to be performed every 4 weeks. Liver function tests such as aspartate aminotransferase and alanine aminotransferase need to be performed every 12 weeks.^[4] If the total white blood cell (WBC) count falls less than 3,500 cells/mm³, platelet count less than 100,000 cells/mm³, or the liver enzymes greater than

Table 4: Outlines the adverse events of systemic corticosteroids

Common	Cushingoid changes: Moon facies Weight gain Fat redistribution Increased acne Suppression of hypothalamic pituitary axis Delay in pubertal growth (children < 15 years) Infections Hypertension Diabetes mellitus Fluid retention Hyperlipidemia Atherosclerosis Osteoporosis Anxiety, mood changes Easy bruising Poor wound healing Gastric ulcerations
Intravenous route	Rapid administration causes arrhythmias, cardiovascular collapse, myocardial infarction, and severe infection
Ocular effects	Cataract Glaucoma/elevated intraocular pressure Myopia Increased susceptibility to infections Myopia Central serous chorioretinopathy Proptosis Papilledema Diplopia, extraocular muscle paresis, ptosis Abnormal electroretinogram(ERG)/visual evoked potential (VEP) Corneal/scleral thinning Eyelid edema Subconjunctival hemorrhage Iris/ciliary body microcysts

Table 5: Immunosuppressives in uveitis

Class	Generic Name	Mechanism of Action	Dose	Side effects	Comments
Antimetabolite	Azathioprine (Immunan, Azoran)	Alters purine metabolism	1mg/kg/day initially; Max: 2.5-4mg/kg/day	Bone marrow suppression, Gastrointestinal upset, Hepatotoxicity	Can be given once daily or as divided dose twice daily
	Methotrexate (Oncotrex, Folistax)	Inhibitor of dihydrofolate reductase	7.5mg/12.5mg/week initially Maximum: 25mg/week PO,SC,IM	Hepatotoxicity, Interstitial pneumonia, cytopenia	Folic acid 1mg/day
	Mycophenolate Mofetil (Cellcept, renadept, mycept)	IMP dehydrogenase inhibitor	500mg bd initially Maximum: 1.5gm bd	Diarrhoea, Nausea, Neutropenia, Infection	Possibly better tolerated than azathioprine
	Leflunomide (Arava)	Di hydro – orotate, dehydrogenase inhibition (pyrimidine synthesis)	100mg qid x 3 days, then 20mg/day		nil
Alkylating agent	Cyclophosphamide (Cytoxan, Endoxan)	Lymphocytotoxicity	2.5mg/kg/day Maximum: 3mg/kg/day	Bone marrow suppression, haemorrhagic cystitis, malignancy (bladder, leukaemia), Infection, Infertility	Can be given as iv pulse
	Chlorambucil	Causing DNA to DNA cross-linking, inhibiting cell replication and protein synthesis	0.1mg/kg/day Maximum:0.2mg/kg/day	Infertility, bone marrow suppression, teratogenic, Infection	nil
T-cell inhibitor	Cyclosporine (Sandimmune, Neoral)	T cell inhibitor	2.5-5mg/kg/day Maximum: 10mg/kg/day	Renal dysfunction, tremor, hirsutism, hypertension, gum hyperplasia	Monitor for renal toxicity, BP
	Tacrolimus (Prograf)	T cell inhibitor	0.15-0.30mg/kg/day	Nephrotoxicity, Hypertension, Neurotoxicity, Hyperkalemia, Hepatitis, Diabetes	Monitor for renal toxicity, BP
	Rapamycin (Sirolimus)	Blocks response to IL-2 & thereby blocks activation of T & B cells	Loading dose 6mg, Maintenance 2mg/day	Increase susceptibility to infection, lymphoma and hyperlipidosis	Subconjunctival & intravitreal injections can also be given
Calcineurin Inhibitor	Voclosporin	Reversible inhibitor T cell proliferation	0.25mg/kg/day -4.5mg/kg/day	Diarrhoea, Headache, Hypertension	
	Colchicine (Colchicindon)	Inhibits neutrophil chemotaxis by inhibition microtubule polymerisation	1.5mg/day	Thrombocytopenia, anaemia, hypokalemia, GI upset, anorexia, rash, hyperlipidemia	

five times of normal level; the immunosuppressive therapy needs to be discontinued.^[18,20] Methotrexate and azathioprine are the commonly used drugs in uveitis. Recently, mycophenolate mofetil is gaining popularity. Voclosporin^[19] and sirolimus^[20,21] are the recently introduced T cell inhibitors with good efficacy.

Methotrexate may also be given as intravitreal injections (400 mg in 0.1 ml).^[22] Sirolimus can be used as subconjunctival or intravitreal injections and are undoing phase 3 clinical trials in noninfectious uveitis.^[23] Alkylating agents are highly toxic with good efficacy and these agents are used in severe cases of necrotizing scleritis and systemic diseases like Wegener's

granulomatosis, etc. In severe or refractory cases of uveitis, more than one drug (e.g., triple immunosuppressive therapy in serpinginous choroditis) can be used to control the inflammation.

Biologics

Table 6 shows the types of biologics available.

Anti-tumor Necrosis Factor-alpha (Anti TNF α) Therapies

TNF- α is a key cytokine involved in the pathogenesis of noninfectious uveitis. Anti TNF α agents used in uveitis

include etanercept, infliximab, and adalimumab. Their mechanism of action, recommended dosage, and side effects of Anti TNF α agents are listed in Table 7.^[24-26] Infliximab and adalimumab seem to be more effective than etanercept for the treatment of ocular inflammation. Reactivation of tuberculosis is a serious complication of anti-TNF therapy. Infliximab is administered intravenously, at a usual dose of 3–10 mg/kg, but doses as high as 10–20 mg/kg have been reported with success and few side effects. Infliximab causes good initial response to therapy in uveitis; however, the effect is temporary and repeated infusions are necessary every 4–8 weeks to maintain remission. Infliximab causes the development of antibodies against the murine component of the molecule. For this reason, we need to use concomitant therapy with an antimetabolite or glucocorticoid to suppress antibody production.

Adalimumab, a recombinant immunoglobulin (Ig)G1 monoclonal antibody targeting TNF- α , showed efficacy both as monotherapy and in combination with other disease-modifying antirheumatic drugs (DMARDs). It has the advantage of self-subcutaneous administration and the recommended dose is 40 mg at 2-week intervals.

Interferons (IFN)

IFN- α is a naturally occurring cytokine secreted in response to viral infections. It causes enhancement of suppressor T cell activity, reduction of proinflammatory cytokine production, and enhancement of phagocytic activity. IFN- α is given as subcutaneous injection daily 6 million units per day initially

and subsequently tapered to 3 million units two to three times a week. Side effects include redness at the site of injection, flu-like symptoms, depression and suicidal behavior, severe cytopenias, cotton wool spots, and retinal hemorrhages in the retina.^[27]

Intravenous Immunoglobulin

Intravenous immunoglobulin has multiple mechanisms of action to enhance the immunity. Main advantage is that it is not associated with systemic immune suppression. Usual dose is 1–2.5 g/kg/cycle every 2–4 weeks until inflammation has subsided. Side effects include thromboembolism, aseptic meningitis, and risk of transmitting blood-borne infections.

Anti-interleukin Therapies

Daclizumab is a humanized monoclonal antibody against the interleukin (IL)-2 receptor.

Nussenblatt *et al.*, described the use of 4-weekly intravenous infusions of daclizumab for treatment of severe sight threatening noninfectious uveitis.^[28] IL-1 receptor antagonist (IL-1RA) is a naturally occurring inhibitor of IL-1. Anakinra is a recombinant human IL-1RA, administered at a daily dose of 100 mg subcutaneously in adults.^[29]

Other Biologic Agents

Alemtuzumab is also known as Campath-1H, is a humanized B monoclonal antibody against the pan lymphocyte antigen CD52. Dick *et al.*, used for 5 consecutive days by intravenous infusion and seems to be an effective treatment for uveitis, leading to long-term remission.^[30]

Rituximab is a mouse-human chimeric monoclonal IgG1 antibody against CD20, expressed by B cells. It is effective against predominantly T cell mediated autoimmune diseases, such as rheumatoid arthritis and Wegener's granulomatosis. Heiligenhaus *et al.*, used rituximab in juvenile rheumatoid arthritis (JRA) associated uveitis, which was refractory to traditional immunosuppressives and TNF- α inhibitors.^[31]

Biologic therapy provides new options for the treatment of refractory uveitis, showing a favorable safety and efficacy profile. However, lack of evidence from randomized controlled studies limits our understanding as to when to start the treatment, which drug to choose, and how long to continue therapy. In addition; high cost, lack of long-term usage, and reactivation of latent tuberculosis limits its use in India.

Table 6: Classification of Biologics

TNF Blockers	Biologics		
	IL-Receptor antagonist	Lymphocyte antagonist	Others
Infliximab	IL 1- Anakinra	Anti CD 52- Alemtuzumab	Interferon -IFN α
Adalimumab	IL 2- Blocker	CD 20 Blocker - Rituximab	Intravenous immunoglobulin (IVIg)
Etanercept		CD 2 Blocker - Alefacept CD 11a Blocker - Efalizumab Selective T cell Co stimulation modulator - Abatacept	

Table 7: Mechanism of action, dosage, and side effects of cytokine inhibitors

	Generic Name	Dosage	Mechanism of action	Side effects
Cytokine Inhibitors	Etanercept (Embrel)	25mg sc twice a week	TNF inhibition: soluble TNF receptor	Sepsis, Lymphoma, autoantibodies, skin reactions
	Infliximab (Remicaide)	3-10mg/kg iv every 4-8 wks	TNF inhibition: TNF α monoclonal antibody	Sepsis, Lymphoma, Autoantibodies
	Daclizumab (Zenapax)	1mg/kg iv Q 2 wks	IL-2 inhibition: IL-2 α receptor antibody	Granulomatous inflammation, Infection

Adjuvant Therapy

To provide symptomatic relief for pain and discomfort and break the posterior synechiae, the following cycloplegics can be used:

1. Short acting cycloplegics:
 - a. Tropicamide (0.5 and 1%) has a duration of 6 hours
 - b. Cyclopentolate (0.5 and 1%) has a duration of 24 hours
2. Long acting cycloplegics:
 - a. Homatropine 2% has a duration of up to 2 days
 - b. Atropine 1% is the most powerful cycloplegic and mydriatic with duration of up to 2 weeks.

Newer Nonsteroidal Anti-Inflammatory Agents: Bromfenac, Nepafenac^[32]

They are used for reduction of ocular pain and inflammation following cataract surgery and in scleral inflammation. It is a potent inhibitor of the cyclooxygenase (COX)-2 enzyme and has a highly lipophilic molecule that rapidly penetrates to produce early and sustained drug levels in all ocular tissues.

Bromfenac ophthalmic solution 0.09%: It can be used (twice daily dosage) as either monotherapy or as an adjunct therapy to steroids.

Nepafenac 0.1%: It is a prodrug. It penetrates the cornea six times faster than diclofenac. It is converted to amfenac in ocular tissues. It has been approved for thrice daily dosage beginning 1 day before cataract surgery.

Current Trends in Infectious Uveitis Management

Toxoplasmosis is the commonest cause of infectious posterior uveitis. Ocular toxoplasmosis is usually managed with systemic antitoxoplasma drugs (Cotrimoxazole-sulphamethoxazole trimethoprim, clindamycin, pyrimethamine, azithromycin, atavouquone, spiramycin) and systemic steroids. Soheilian *et al.*, used intravitreal clindamycin (1 mg/0.1ml) along with dexamethasone (0.4 mg/0.1ml) to control the ocular inflammation.^[33]

In tropical countries, fungal infection is commonly seen. Recently voriconazole (oral dose 200 mg twice a day) and intravitreal voriconazole (50–100 g in 0.1 ml) can be used to treat the fungal infection in the eyes.^[34]

In ocular tuberculosis, there may be paradoxical worsening of inflammation following antitubercular therapy and systemic steroids. If the inflammation is progressing inspite of addition of oral steroids, immunosuppressives may be added with close monitoring of liver function.^[35]

In viral uveitis, ganciclovir gel (0.15%) is used topically to control the cytomegalovirus anterior uveitis^[36] and intravitreal ganciclovir implants can be used to treat cytomegalovirus retinitis.^[37]

Anti-vascular Endothelial Growth Factor (anti-VEGF) Therapy

The use of intravitreal anti-VEGF therapies, namely bevacizumab (1.25 mg in 0.05 ml) and ranibizumab (5 mg/0.05 ml) has been described in the treatment of uveitic complications

such as cystoid macular edema, choroidal neovascularization, and retinal neovascularization.^[38]

Conclusion

Corticosteroids still remain the mainstay of treatment in uveitis. Immunosuppressives have revolutionized the treatment in chronic uveitis. Better understanding of immunology and uveitic diseases help providing more targeted treatment in uveitis. The future thus holds great promise for uveitis with continuing development of newer drugs.

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