

Review Article

IMMUNOSUPPRESSIVE DRUG THERAPY IN UVEITIS

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ABSTRACT

The treatment of non-infectious uveitis is often a challenge to the treating ophthalmologist. Though the acute phase can be controlled by frequent and high doses of topical and systemic steroids, in some situations, uveitis can be chronic or recurrent and can lead to permanent structural damage and blindness. Chronic use of corticosteroids is known to increase the risk of adverse effects such as cataracts, glaucoma, diabetes, hypertension, hyperlipidemia and osteoporosis. This led to introduction of immunosuppressive chemotherapeutic medications in the care of patients with progressive blinding uveitis. Yet, many ophthalmologists are reluctant to use immunosuppressive therapies as they are considered more of cancer therapy drugs with considerable side effects. This review highlights the role of immunosuppressive drug therapy in uveitis including their uses and possible adverse effects.

Key words: Uveitis, steroids, chemotherapy, anti-cancer drugs, immunosuppressive drugs.

INTRODUCTION

Uveitis can be classified in many ways, but the anatomical classification based on the primary location of maximal inflammatory activity has the maximal clinical utility. Uveitis can be infectious or non-infectious in origin. The two important goals of treatment of uveitis are complete elimination of all active inflammation and decrease the steroid requirement. Currently available management options for non-infectious posterior uveitis include corticosteroids delivered by periocular or oral routes. Vast encouraging experience with immunosuppressive medications in the fields of rheumatology and nephrology has encouraged uveitis practitioners to consider

the option of immunosuppressive therapy in ocular inflammatory disorders.

Approximately 5-20% of legal blindness in developed countries is due to uveitis [1]. In India, in a tertiary referral eye care centre, uveitis accounted for 1.5% of new cases [2]. Immunosuppressives have proven useful and even sight saving in patients with severe ocular inflammatory disease. These drugs may even be used to reduce or eliminate the need for corticosteroid therapy. In general, their use is reserved for severe, sight threatening cases of uveitis that are poorly responsive to corticosteroids. These drugs are also referred to as steroid sparing or steroid equivalent drugs [3, 4, 5, 6].

Classification of Immunosuppressive drugs:

- ❖ **Antimetabolites:** Azathioprine, methotrexate, and mycophenolate, mofetil, leflunomide.
- ❖ **T-cell inhibitors:** Cyclosporine, tacrolimus.
- ❖ **Alkylating agents:** Cyclophosphamide, chlorambucil
- ❖ **Newer agents:** Daclizumab, adalimumab, alemtuzumab, rituximab, etanercept, infliximab, abatacept, interferons.

Indications: A suggested categorization of indications of immunosuppressive agents in the treatment of uveitis suggested by the international uveitis study group is as following:

Category	Disease
Absolute	Behcet's syndrome Vogt-Koyanagi-Harada syndrome Sympathetic ophthalmia Rheumatoid sclerouveitis
Relative	Intermediate uveitis Retinal vasculitis with central vascular leakage Severe chronic iridocyclitis or panuveitis JRA related iridocyclitis Children with intermediate uveitis

Patients who suffer intolerable side effects of corticosteroid therapy are another group of indications for the same.

These are also indicated in cases with chronic uveitis and scleritis not responding to low dose corticosteroids or that require a fairly high dose of corticosteroids for more than 6-12 months.

Prerequisites before starting Immunosuppressive treatment

- Informed consent should be obtained from patient.
- Collaboration with oncologist or hematologist is very often required.

Systemic work up:

- Complete hemogram with platelet count
- Urinalysis
- Liver function test (including liver enzymes- ALT, AST)
- Renal function test (Serum creatinine, blood urea)
- Electrolytes levels.

Immunosuppressive drugs, Dosage and adverse effects:**Antimetabolites**

Methotrexate (MTX): Methotrexate is an anti-metabolite and antifolate drug which acts by inhibiting the enzyme dihydrofolate reductase, leading to inhibiting formation of thymidylate which inhibits DNA replication and RNA transcription and thereby inhibits the proliferation of rapidly dividing immune cells.

Dose: Available as 2.5mg tablet and i/m or s/c injections. Injection dose- 7.5-2.5mg/week in a single undivided dose. Folate 1mg/day to be given concurrently.

Use: MTX is used as first choice in pediatric uveitis. It is also very helpful in JIA and sarcoidosis [7]. MTX is a good option as primary treatment or as a steroid sparing adjuvant.

Adverse effects: Hepatotoxicity is a common serious side-effect. Commonly liver function tests may be elevated to twice normal levels which warrants dose reduction or discontinuation [8]. Other side effects are intestinal pneumonitis, cytopenias and gastrointestinal side effects.

Azathioprine: Azathioprine is a prodrug, which after ingestion is converted to 6-mercaptopurine, a competitive inhibitor of purine synthesis. Azathioprine blocks both DNA replication and RNA synthesis, thereby inhibiting the proliferation of actively dividing cells.

Dose: Available as 50mg tablets. Started 1.5-2mg/kg/day as a single morning dose; maximum of 2.5-4mg/kg/day.

Use: It is used most often as a corticosteroid sparing agent in chronic inflammatory eye disease that affects adults and elderly patients such as Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, Behcet's disease and serpiginous choroiditis [7,8].

Side-effects: The most common side effects are nausea and anorexia. Other uncommon side effects are hepatotoxicity, myelosuppression with leukopenia and thrombocytopenia. Secondary malignancies like lymphomas have been reported but are rare in occurrence.

Mycophenolate mofetil (MMF): It is a selective inhibitor of Inosine monophosphate dehydrogenase that interferes with guanosine nucleotide synthesis.

Dose: Available as 250/500mg capsules or 200mg/ml oral suspension. Given in dose of 500mg BD increased to 1gm BD; maximum dose: 1.5 gm BD.

Use: MMF is safe for long term use and is recommended for treatment of refractory panuveitis or posterior uveitis with uncontrolled inflammation despite high prednisolone maintenance dosage (>15mg/day) or toxicity [9,10,11].

Side-effects: the most common side effects are gastrointestinal including diarrhea and vomiting. More severe, but less common side effects include leucopenia, sepsis and secondary malignancies.

Leflunomide: Leflunomide inhibits pyrimidine synthesis by inhibiting the enzyme dihydro-reductase dehydrogenase. The drug also inhibits cytokine and growth factor receptors associated with tyrosine kinase activity.

Dose: 100mg QID for 3 days; then 20mg QID maintenance dose

Side-effects: The most serious side effect of leflunomide therapy include liver toxicity and leukopenia, both of which are reversible. Other common side-effects include diarrhea, dyspepsia, abdominal pain, rash and reversible alopecia [12].

T cell inhibitors

Cyclosporine (CSA): It appears to preferentially affect immunocompetent T cells that are in the G₀ and G₁ phase of the cell cycle and its effect appears to be specific transcriptional inhibition in these cells blocking replications as well as their ability to produce lymphokines such as interleukin-2.

Dose: Available as 25/50/100mg capsules or 100mg/ml oral suspension. 2.5-5.0mg/kg per day in divided doses; maximum dose: 10mg/kg per day.

Use: CSA is administered most often to treat moderate to severe bilateral sight threatening uveitis which have become steroid dependent or steroid intolerant. Indications are panuveitis of various etiologies, parsplanitis or JRA [13, 14, 15].

Side-effects: The long term use of CSA is limited by the development of neurological side effects, hirsutism, gingival hyperplasia, gastro-intestinal disturbances, breast tenderness, hyperglycemia, hepatotoxicity.

Tacrolimus (FK506): Tacrolimus binds to immunophilin FKBP-12 creating a complex FKBP12-FK506. This complex interacts

with and inhibits calcineurin, thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription.

Dose: Available as 0.5mg, 1mg, 5mg capsules, 5mg/ml oral suspension. It is given in dose of 0.05mg/kg/day in uveitis.

Use: Tacrolimus is used in cases of chronic posterior uveitis with low doses of steroids and in CSA resistant cases [16].

Side-effects: The prevalence of cardiovascular toxicity, hypertension, hypercholesterolemia and diabetes mellitus were all less with relatively low dose therapy. Other common side effects include nephrotoxicity, neurotoxicity, myopathy, gastro-intestinal disturbances and hepatotoxicity, which may need dose reduction or discontinuation.

Alkylating agents

Cyclophosphamide: It is nitrogen mustard alkylating agent, the active metabolite of which alkylate purines in DNA and RNA, resulting in cross linking, aberrant base pairing, ring cleavage and depurination. This process results in cell death. Cyclophosphamide is toxic to both resting and dividing lymphocytes. It inhibits both humoral and cell mediated immunity.

Dose: Available as 25/50mg tablet. Oral: 1-3mg/kg/day.

Use: It is very helpful in severe sight threatening or refractory uveitis that is not responding even to high dose pulse steroid therapy [7, 17] e.g. Bechet's affecting retina, serpiginous choroiditis and sympathetic ophthalmia. It is also very useful in uveitis associated with Wegener's disease and polyarthritis nodosa as it takes care of both ocular and systemic disease.

Side-effects: The most common side effect is bone marrow suppression. Other significant side effects are hemorrhagic cystitis [18], gonadal toxicity [19], nausea, vomiting and reversible alopecia, increased risk of carcinoma bladder and hematopoietic malignancies [20].

Chlorambucil: It causes DNA to DNA and DNA to protein cross linking which leads to interference in DNA replication, DNA transcription and nucleic acid function.

Dose: There are two approaches to the use of chlorambucil:

- a- 0.1-0.2mg/kg/day as single dose followed by maintenance therapy continued for a year.
- b- Short term high dose therapy: 2mg/day for one week; escalation by 2mg per day every week for a duration of 3 months.

Use: Chlorambucil is used in severe vision threatening uveitis refractory to other modes of treatment [21] like in cases of posterior uveitis e.g. Bechet's disease [22], VKH [23], sympathetic ophthalmia, serpiginous choroiditis [24] and retinal vasculitis. It is also helpful in pars planitis, anterior uveitis like JRA and HLA B27 associated uveitis [25].

Side-effects: The most common side effects of chlorambucil is severe leucopenia. It can be associated with unpredictable and sudden pancytopenia. Other side effects include increased risk of secondary gastro-intestinal and skin cancers, infertility, risk of serious infections and gastro-intestinal upset.

Newer agents

Daclizumab: Daclizumab is an IgG monoclonal antibody that specifically binds to the Tac subunit of the human IL-2 receptor expressed on activated T cells. It functions as a specific IL-2 receptor antagonist.

Dose: 1mg/kg every 2 weeks i.v.

Side-effects: Commonly reported side effects include psoriaform skin rashes, lymphadenopathy, mild peripheral edema and infections.

Adalimumab: Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor alpha.

Dose: Available as 1ml prefilled glass syringe. Each syringe delivers 0.8ml (40mg) of drug. It is administered by subcutaneous injection at a dose of 40mg every 2 weeks.

Use: It is used in treatment of chronic refractory childhood uveitis and Behcet's disease [26, 27, 28].

Side-effects: The most common side effect of Adalimumab is a self-limiting injection reaction.

Alemtuzumab: Alemtuzumab is a humanized monoclonal antibody directed against CD52, a molecule found on the surface of lymphocytes and monocytes. There are reports of treatment of ocular inflammatory disease with Alemtuzumab [29, 30]. However, there was high incidence of infusion reactions and hematological toxicity.

Rituximab: Rituximab is a chimeric mouse/human monoclonal antibody that acts against the B cell antigen CD20. It is found to be effective in treatment of a chronic refractory endogenous anterior uveitis refractive to corticosteroids and systemic autoimmune disease [31, 32, 33, 34].

Abatacept: Abatacept is a soluble fusion protein composed of the ligand binding domain of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and a fragment of human immunoglobulin [35]. CTLA-4 is normally expressed on the surface of T-cells and prevents the stimulation of these cells via the CD80/86 co-stimulation pathway. It is the first of new class of drugs called co-stimulation blockers.

Etanercept: It is tumor necrosis factor (TNF) antagonist and is a recombinant protein made up of two soluble TNF receptors and Fc portion of human IgG. A competitive inhibitor, it binds and inactivates TNF.

Dose: 25mg subcutaneously twice weekly.

Use: It is approved for use in rheumatoid arthritis. It has not been comprehensively studied in uveitis.

Side-effects: Common side effects are formation of auto-antibodies and skin reaction.

Infliximab: Infliximab is a chimeric (murine-human) monoclonal antibody that binds both circulating and membrane-bound TNF- α .

Dose: 3-10mg/kg i.v. every 4-8 weeks.

Uses: Behcet's uveitis [36], refractory posterior uveitis [37], chronic uveitis macular edema [38], juvenile idiopathic arthritis [39], posterior segment neovascularization [40].

Side-effects: Autoantibodies formation, infusion reaction, upper respiratory tract infection, urinary tract infection, rarely pneumonia, cellulitis and sepsis. Reactivation of latent tuberculosis [41], congestive heart failure [42], and exacerbation or initiation of demyelinating disease [43], reactivation of hepatitis-B, lymphomas, pancytopenias, hepatotoxicity.

Interferon 2 alpha: Interferons have antiviral, antineoplastic, immunomodulatory and anti-angiogenic effects. It is used in treatment of refractory and sight threatening uveitis including both Behcet's and non-Behcet's cases [44]. Common side effects are flu like symptoms, elevation of LFT, alopecia, neutropenia, lymphocytopenia and thrombocytopenia.

CONCLUSION

Corticosteroids remain the mainstay of therapy in patients with uveitis. Prolonged therapy, higher doses of corticosteroids have significant side effects. Immunosuppression may be required to taper the doses of corticosteroids or when the inflammation has responded poorly to corticosteroids alone. Immunosuppression requires diligent management and is best co-managed with a

rheumatologist or uveitis specialist and an oncologist.

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