IMMUNOSUPPRESSIVES IN UVEITIS

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INTRODUCTION

Uveitis is classified in many ways and 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. Specific antimicrobial agents along with anti-inflammatory medications form the basis of therapy in infectious uveitides. Non-infectious uveitic entities form a group of rare ocular inflammatory disorders with some of them involving sight is especially more concerning in cases of posterior uveal involvement. In some of the conditions like Behcet's disease and collagen vascular disorder associated uveitis, there can be associated threat to life as well.

The immune system functions to defend against foreign substances, infectious agents and tumors. Host tissues are usually recognized as self and not attacked. However, if the immune response is too exuberant and damages host tissues, or if an autoimmune response develops, immunomodulation or immunosuppression is required.

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 immunosupressive therapy in ocular inflammatory disorders, which may require immunomodulation for prolonged periods.

History of Development of Immunosuppressive Agents: In April 1949, Hench and colleagues reported beneficial effect of 17-hydroxy-11-dehydro corticosterone in 14 patients with rheumatoid arthritis[1]. All patients had moderate to marked improvement in their disease. By the following year the therapeutic effect of corticosteroids for uveitis was clearly demonstrated by a number of groups[2,3]. Corticosteroids remain the mainstay of therapy for uveitis. However, many patients have corticosteroid-resistant disease or develop intolerable adverse effects to steroids. Additionally, in patients requiring long-term therapy with corticosteroids, it is often prudent to add another immunosuppressive, steroid-sparing agent to the therapeutic regimen so that lower dosages of corticosteroids can be used. The combination of corticosteroids and immunosuppressive agent may be a better therapeutic approach than using an immunosuppressive agent alone without corticosteroids.

As a result of the need for effective immunosuppression for patients undergoing organ transplantation, a large number of immunosuppressive agents became available. The history of discovery of these agents is quite interesting. Use of sulfur mustard during World War I had devastating effects, causing leukopenia in survivors and lymphoid aplasia in those who died.[5] Currently available alkylating agents were first synthesized based on these findings in 1954. Initial studies on the applications of purine bases was done by Hitchings and co-workers in 1960[4]. Although cyclosporine was initially studied for its antifungal activity[6] and potential antimalarial activity[7], this agent has been the center of much attention since Borel and colleagues[8] reported its effective suppression of several immune-mediated functions. Between the years 1979-1982 several workers reported the usefulness of cyclosporine in the field of transplantation immunology.[9-12]

Immunosuppressives have proven useful and even sight saving in patients with severe ocular inflammatory diseases. 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 and are of equivalent or only slightly greater potency than steroids.[13-16]

Indications:

A suggested categorization of the indications of immunosuppressive agents in the treatment of uveitis suggested by the International Uveitis Study Group is:

Category	Disease
Absolute	Behcets syndrome VKH syndrome, Sympathetic Ophthalmia, Rheumatoid sclerouveitis
Relative	Intermediate uveitis Retinal vasculitis with central vascular leakage Severe chronic iridocyclitis or panuveitis JRA related iridocyclitis
Questionable	Children with intermediate uveitis

Patient who suffer intolerable side effects of corticosteroids therapy are another group of indications for the same. Also are 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.

Immunosuppressive drugs can be grouped as:

Antimetabolites : Azathioprine, Methotrexate and Mycophenolate mofetil

T-cell inhibitors : Cyclosporine, Tacrolimus

Alkylating agents: Cyclophospamide, Chlorambucil

Newer agents: Daclizamb, Etanercept, Infliximab

I. ANTIMETABOLITES

1. Azathioprine

Mechanism of action:

Azathioprine ia a purine nucleoside analogue. Azathioprine ® 6-mercaptopurine (active form) ® thioinosinic and thioguanilic acid interfere with DNA replication / RNA transcription**.**This causes chromosomal breaks when incorporated into DNA leading to aberrant protein synthesis.

Immunologically, it decreases the number of peripheral T and B lymphocytes, reduces mixed lymphocyte reactivity, interleukin-2 synthesis and Ig M production.

Dose : available as 50 mg tablets; started 1.5 to 2 mg/kg/ day as a single morning dose; max of 2.5 to 4 mg/kg/day

Onset : anti inflammatory action takes at least 3-4 weeks and even upto 3 months. Dosage of steroids should be tapered only once the anti-inflammatory action is seen.

Side effects

- Reversible bone marrow suppression
- Increased risk of malignant disease (especially Non Hodgkin's Lymphoma)
- Hepatotoxicity (<2%) , life threatening hepatic vasocclusive disease (rare).
- Gastrointestinal intolerance – most common (25% of patients)

Monitoring

- CBC including platelet count every 3-4 weeks.
- Caution if WBC count < 3500 per cu. mm or platelet below 125000 per cu. mm.
- LFT every 12 weeks.
- If levels elevated above 1.5 times upper limit of normal , decrease dose by 25 to 30 mg per day and re-evaluate after 2 weeks. If marked elevation i.e. > 5 times of upper limits, discontinue.

Contraindications

- Preexisting hepatic disease
- Pregnancy
- Active bacterial, fungal, viral or protozoal infections

2. Methotrexate

Mechanism of action

Methotrexate is a folic acid analogue; it inhibits the enzyme dihydrofolate reductase reversibly which is responsible for the conversion of dihydrofolate to tetrhydrofolate. This action inhibits the production of thymidylate that is essential for DNA replication. As such, it inhibits rapidly dividing cells, such as leucocytes which produces an anti inflammatory effect.

Among other indications common to the immunosuppressives, it is relatively safe for use in children.

Dose: available as a 2.5 mg tablet and also as injections via I/M or S/C route to be given 7.5- 25 mg / week in a single undivided dose (0.1 -0.5 mg/kg per week)

Folate – 1 mg/ day given concurrently

Onset: Action starts after 3to4 weeks and takes 6to8 weeks for complete effect to come. So corticosteroids are not tapered immediately.

Side effects

- Hepatotoxicity – abnormal LFTs occur in 20% cases; liver cirrhosis in 0.1%
- Cytopenia
- Ulcerative stomatitis occurs in in 20% of patients
- Nausea, anorexia, GI bleeding
- Dermatological side effects like urticaria, pruritus, alopecia, erythema multiforme and exfoliative dermatitis
- Pneumonitis and pulmonary fibrosis
- Increased risk of secondary malignancy

Monitoring

- CBC, LFT, HbsAg, HCV at initiation of therapy
- CBC and platelet counts: WBC count below 3500 per cu. mm and platelets below 125,000 per cu. mm – discontinue or lower dose.
- LFTs every 1- 2 months – if elevated above 2 times normal – discontinue or lower dose
- Liver biopsy if LFTs still elevated after discontinuation
- Abstain from alcohol

Contraindications:

- Pregnancy and lactation
- Neutropenia and thrombocytopenia
- Pre-existing liver disease

3. Mycophenolate Mofetil

Mechanism of action:

Is a selective inhibitor of Inosine monophosphate dehydrogenase that interferes with guanosine neuclotide synthesis. Major effects on T and B lymphocytes. It does not suppress IL 2 but does seem to be able to inhibit CD4 or CD8 positive T cell macrophage interactions and macrophage migration.

Dose : 500 mg BD increased to 1 gm BD; max dose :1.5 gm BD, available as 250/ 500 mg capsules /200mg/ ml oral suspension to be ingested in empty stomach. Metabolized into an active compound -mycophenolic acid which is excreted renally.

Onset : 2 weeks to 3 months.

Side effects

- GIT problems (nausea, vomiting, pain, diarrhea)
- Leukopenia
- Lymphoma
- Non melanoma skin cancers
- Opportunistic infections e.g. CMV and HSV infections
- Myalgia, fatigue, headache, nausea

Monitoring

- CBC weekly for 4 weeks ; twice monthly x 2 months ; monthly thereafter
- LFTs every 3 months

Contraindications

- To be used with caution in patients with renal disorders and those with GIT disturbances.

4. Leflunomide

Mechanism of action

Inhibits pyrimidine synthesis by inhibiting the enzyme dihydroreductase dehydrogenase. Activated T cells are particularly susceptible to this drug as they synthesize their pyrimidines by primarily using this enzyme. The drug also inhibits cytokine and growth factor receptors associated with tyrosine kinase activity.

Dose : 100mg QID x 3 days; then 20 mg QID

Onset : 2 weeks

Side effects:

- Cytopenias
- Fetal loss
- Diarrhoea
- Hypertension

Contraindications

- Pregnancy

Its role had not however been studied in uveitis

Preliminary data have shown it can inhibit experimental autoimmune uveitis

II. T- CELL INHIBITORS

1. Cyclosporine

Mechanism of action

Cyclosporine is a natural product of various fungi the most notable being *Tolypocladium inflatum Gams*. It appears to preferentially affect immunocompetent T cell 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 :2.5 – 5.0 mg/ kg per day in divided doses; max : 10

mg/kg per day, available as 25/50/100 mg capsules or 100 mg /ml oral suspension (microemulsion). The microemulsion form has a better bioavailability than the capsules. Oral solutions dispersed in milk or fruit juice, have poor absorption and peak levels reached 6-8 hours after administration.

Onset : 2 – 6 weeks

Side effects

- Nephrotoxicity
- Hypertension
- Hepatotoxicity
- Gingival hyperplasia
- Myalgias
- Tremor
- Parasthesias
- Hypomagnesemia
- Hirsuitism

Monitoring

- Check BP at every visit and not less than monthly initially and 3 monthly on long term follow up.
- Serum creatinine every 2 weeks initially and every month once dosage stabilized

Contraindications

- Pre existing malignancies
- Severely compromised renal functions
- Use with caution in pregnant women

2. Tacrolimus (FK 506)

Mechanism of action

A macrolide antibiotic synthesized by S*treptomyces tsukubaensis*, it inhibits the activation of T lyphocytes similar to that of cyclosporine.

Dose : oral : A dose of 0.05 mg/kg/day in uveitis ; 0.10 - 0.15mg/kg/day is used in liver transplants, available as 0.5 mg, 1 mg, 5mg capsules, 5mg / ml oral suspension. Absorption variable and incomplete; better in empty stomach, can be given I/V but anaphylaxis has been reported with this route.

Tacrolimus is most effective early in the course of the therapy, but its effectiveness may decrease gradually with prolonged treatment.

Side effects

- renal impairment
- neurological symptoms
- hyperglycemia
- hyperglycemia
- tremor, headache, trouble sleeping
- parasthesias
- hypertension
- GIT symptoms

FK 506 is not administered with cyclosporine as the toxicity is additive.

Monitoring

- Weekly – LFTs, BUN, Serum Creatinine, Electrolytes including Ca, Mg and PO4, Cholesterol and triglycerides, Glucose and CBC. With stable dosing, the frequency may be reduced to monthly.
- BP monitored at every visit, at least monthly initially and 3 monthly thereafter.

III. ALKYLATING AGENTS

1. Cyclophosphamide

Mechanism of action

Is a nitrogen mustard alkylating agent, the active metablites 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, because the cells are unable to replicate. Cyclophosphamide is cytotoxic to both resting and dividing lymphocytes. It inhibits both humoral and cell mediated immunity.

Dose : Oral : 1-3 mg/kg/day; available as a 25/50 mg tablet. It is used intravenously as a pulse therapy when immediate effect is required – the dose is 40 -50 mg /kg I/V, followed by maintenance therapy once or twice a week. Fluid intake should be increased to promote frequent voiding and decrease the length of time the drug stays in the bladder.

Onset: Although the total effect takes 2 -9 weeks to establish, it has a comparatively rapid onset of action.

Cyclophosphamide is considered for use in severe sight threatening inflammation, responding poorly or patients who cannot tolerate corticosteroids. It is the drug of choice and has been used extensively in Wegners Granulomatosis. The use of cyclophosphamide is generally restricted to 6 – 12 months, as the risk of chromosomal damage has been shown to increase after prolonged therapy.

Side effects

- bone marrow suppression; myelodysplasia seen

with long term therapy
- Opportunistic infections
- hemorrhagic cystitis-manifests initially as microscopic haematuria; can use concomitant 2 - mercaptopurine sulphonate therapy to avoid bladder toxicity
- teratogenecity
- ovarian suppression, testicular atrophy and azoospermia
- alopecia(reversible)
- Nausea, vomiting
- interstitial pulmonary fibrosis

Monitoring
- CBC, platelet count, urinalysis – weekly; once dosing stable- every 4 weeks

Contraindications
- Pregnancy
- Lactation
- Underlying malignancy
- Severe bone marrow depression

2. Chlorambucil

Mechanism of action

It inhibits protein cross linking in DNA synthesis, which leads to interference in DNA replication, DNA transcription and nucleic acid function

Dose : there are 2 approaches to the use of chlorambucil:

a. 0.1-0.2 mg per day (6 -12 mg daily) as a single daily dose; maintainence therapy continued for a year
b. short term high dose therapy : 2 mg / day x 1 week ; escalation by 2 mg per day every week; duration : 3 – months.

Onset : 4 -12 weeks

Side effects
- Potentially carcinogenic
- bone marrow suppression; rarely, irreversible bone marrow aplasia
- opportunistic infections particularly viral such as herpes zoster may occur
- permanent sterility occurs in men; amenorrhea in women
- anorexia, weakness, emesis

Monitoring
- CBC weekly initially, once dose stabilized, monthly

Contraindications
- pregnancy
- lactation
- underlying neutropenia or thrombocytopenia

IV: NEWER HORIZONS

CYTOKINE INHIBITORS

Cytokines such as IL-2 and TNF have been implicated in the pathogenesis of inflammatory disease. Selective blockade of these has therefore been suggested as a mechanism for modulating inflammation.

1. **Daclizumab**

Mechanism of action

A humanized IL-2 receptor monoclonal antibody, it is 90% human and 10% murine. Daclizumab binds with the TAC subunit of the IL-2 receptor thereby inhibiting IL-2 binding. Since the TAC subunit is expressed only on activated lymphocytes, it is these active cells which are most susceptible.

Dose : 1 mg / Kg every 2 weeks I/V

It has been studied in a small series of patients with severe chronic intermediate and posterior uveitis. It may hold promise for the treatment of autoimmune uveitis.

Side effect : Granulomatous inflammation, infection, cost.

2. Etanercept

Mechanism of action

Is a tumor necrosis factor antagonist. Is a recombinant protein made up of two soluble TNF receptors and the Fc portion of human IgG. A competitive inhibitor, it binds and inactivates TNF.

Dose : subcutaneously twice weekly (25 mg);Onset of action : 1-8 weeks

Approved for use in rheumatoid arthritis, it has not been comprehensively studied in uveitis. However, there is anecdotal evidence that it may be of benefit.

Side effects : Sepsis lymphoma, autoantibiodies, skin reactions and cost.

3. Infliximab

Mechanism of action

Is a chimeric human – murine antibody to TNF that blocks receptor binding.

Dose : given I/V over 2 hours (3mg / kg/ day) every 8 weeks

Approved for the treatment of Crohns disease but has not yet been studied in uveitis.

Side effects : Sepsis, lymphoma, autoantibodies, cost.

4. Interferon 2 alpha:

Interferons have anti viral, antineoplastic, immunomodulatory and anti angiogenic effects. Severe panuveitis as in Behcets disease refractory to conventional corticosteroid and immunosuppressive therapy has led to further search for newer agents and interferon alpha is being evaluated as an alternative therapy for the same.

Mechanism of action

The exact mechanism of action is unknown but probable mechanisms include a direct effect on infectious triggers, enhancement of T-cell and natural killer cell cytotoxicity, and inhibition of endothelial cell proliferation.

Dose : 9 million units thrice a week followed by a maintainence dose of 3 million units thrice a week. Dose however is still a controversy.

Side effects

- flu like symptoms
- elevation of LFT
- alopecia
- neutropenia
- lymphocytoenia
- thrombocytopenia

However, the response to interferon 2 alpha is still found to be variable and it has been used primarily in Behcet's disease. Further studies are still required to establish the benefit and appropriate dose.

V. CORTICOSTEROIDS:

Corticosteroids are used with great benefit for inflammatory diseases of a non infectious cause. Their clinical utility is limited by side effects attendant to chronic corticosteroid use, particularly in children who have not completed their growth.

Mechanism of action

In humans, they are not considered to be cytotoxic agents. The steroid combines with the appropriate receptor on the cell surface and then complexes with it in the cytoplasm of the cell. This complex then migrates to the nucleus, where it exerts it's effect on DNA transcription, leading to changes in RNA production, resulting in changes in protein production and cell function.

Effects on the immune system are both local and systemic. The anti-inflammatory actions of corticosteroids involve phospholipase A2 inhibitory proteins called lipocortins which control the biosynthesis of inflammatory mediator, such as prostaglandins and leukotrienes by inhibiting the release of arachidonic acid. The phenotypic effects of corticosteroids include inhibition of leucocyte infiltration at the site of inflammation, and suppression of humoral immune responses. These changes result in a dose dependent reduction in the immune response.

Suggested guidelines for use :

Parameter	Suggested guideline
Initial dose Max adult oral dose Maintenance dose (adult)	1 -1.5 mg/ kg/ day 60-80 mg / day $\leq$ 10mg / day
Tapering schedule	Over 40 mg/ day , decrease by 10 mg/ day every 1-2 wks 40-20 mg/ day, decrease by 5 mg/ day every 1-2 wks 20-10 mg/ day,decrease by 2.5mg/ day every 1 -2 wks 10-0 mg/ day, decrease by 1-2.5 mg/ day every 1-2 wks
Monitored	BP, weight, glucose every 3 months Lipids(cholesterol and triglycerides) annually Bone density within the first 3 months and annually thereafter
Supplemental treatment	Calcium 1500mg daily and vitamin D 800U annually Estrogens and antiresorptive agents as needed

If the inflammation exacerbates during the tapering schedule, resume a higher dosage for another month or until the disease is quiet and taper back to just above the threshold at which the disease exacerbated.

Intravenous corticosteroids i.e. methyl prednisolone are usually reserved for emergency cases such as retinal vasculitis, optic neuritis or necrotising scleritis where other agents may work too slowly to preserve vision. The usual dose is 0.5 -1 gm given I/V over 30-60 minutes daily for three days.

Topical steroids penetrate well only into the anterior segment of the eye and are useful in the management of anterior uveitis and episcleritis.

Periocular corticosteroids are useful in the management

of intermediate uveitis associated with decreased vision; the management of macular edema in association with panuveitis or posterior uveitis, and in selected other situations.

Side effects

- Adrenal suppression which may last for 12 months after discontinuation of corticosteroids.
- Symptoms of infections get masked
- Reactivation of tuberculosis
- Hyperglycemia
- Myopathy and myalgias
- Impaired wound healing
- Osteoporosis
- Hyperlipidemia
- Atherosclerosis
- Hypertension
- Spontaneous bone fractures such as vertebral compression or avascular necrosis of the femoral and humeral heads
- Growth retardation in children
- Appetite stimulation and weight gain
- Esophageal ulceration and gastritis
- Mood lability, depression, anxiety, euphoria and psychosis
- Acne vulgaris, facial erythema, striae, hirsuitism, spontaneous ecchymosis
- increased tendency to thrombosis and thromboembolism
- Pancreatitis
- Rapid intravenous administration of methyl prednisolone has been reported to induced arrhythmia, cardiovascular collapse, myocardial infarction and severe infection.

Studies of patient with rheumatoid arthritis have suggested that long term corticosteroid therapy (several years) may be associated with an increased mortality.

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