Steroids and Immunosuppressives in Ophthalmology

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For many years in the past, natural and synthetic corticosteroid preparations were the only therapeutic agents available for immunosuppression. With the advent of other immunosuppressives in 1960’s, they are beginning to occupy an increasingly important role in the management of ocular inflammatory, immune mediated diseases and in cases of severe corticosteroid unresponsive ocular inflammation. The use of immunosuppressive agents by ophthalmologists has greatly increased over the past three decades. This has been mainly possible because of better understanding of the immunopathology of many ocular disorders and the complex pharmacologic and therapeutic properties of these immnosuppressives and their use, in conditions other than in the treatment of malignant neoplasms. Earlier their use was limited to the treatment of corticosteroid resistant sight threatening ocular diseases. Today these drugs occupy the first line in management of diseases like Wegener’s granulomatosis and Behcet’s disease, by inducing long term remission and cure.

**Corticosteroids**

**Mechanism of action**

Corticosteroids inhibit the cyclooxygenase and lipooxygenase pathways by inhibiting phospholipase A₂ thereby inhibiting the release of arachidonic acid.

1. **Antiinflammatory Effects:**
   - Neutrophils:
     - Inhibit neutrophil migration
     - Decreases neutrophil adherence to vascular endothelium
     - Decreases bactericidal activity of neutrophils
   - Mononuclear Phagocytes:
     - Inhibits chemotaxis
     - Decreases clearance of antibody coated particles
     - Reduces production of IL-1 and TNF α
   - Lymphocytes:
     - Redistribution of T lymphocytes (CD4>CD8)
     - Inhibit T lymphocyte activation, proliferation and lymphokine production
     - Inhibit IgG production by B cells
   - Other Effects:
     - Decreases oedema, neovascularisation, serum IgG and IgA and reduces complement concentration.

2. **Immunosuppressive Effects:**
   - Mononuclear Phagocytes:
     - Inhibits chemotaxis
     - Decreases clearance of antibody coated particles
     - Reduces production of IL-1 and TNF α
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The indications for steroid therapy in Ophthalmology are given in Table 1. There are three ways in which steroids can be effectively used in the treatment of uveitis.

**A) Corticosteroid Drops**

It is imperative that initial treatment of anterior uveitis
be aggressive. Initially, hourly instillation during waking hours is advisable. Once the eye responds to treatment as evidenced by a decrease in the flare and cells in the eye, a slow tapering of the drops is advised.  

**Hydrocortisone acetate 2.5%**  
**Prednisolone acetate 0.12% (Predforte – 1%)**  
**Dexamethasone phosphate 0.1%**  
**Fluorometholone 0.1% - FML, 0.25% - FML forte**  

Side Effects: Glaucoma, Posterior subcapsular cataract, [Drug related] Scarring between conjunctiva and globe  
Subdermal fat atrophy, Posterior uveitis, Increased predisposition to infections – herpes, fungal, Dermatitis, Delayed wound healing

**B) Injection**

**1) Periocular Injection**

This permits relatively high concentration of the drug to be given rapidly and ensures delivery of the drug to the site of pathology.

**Indications:** Resistant anterior uveitis, Intermediate uveitis, Pars planitis, Posterior uveitis, Cystoid macular oedema, Patients in whom systemic steroids are contraindicated

**Dose:** Depo-Medrone (0.6 ml of 80 mg/ml solution)  
(Methyl prednisolone acetate) or  
Triamcinolone acetonide (Kenalog)  
Inject every 2 weeks, if there is response to the first 2 to 3 injections

**Side Effects:**  
- Posterior subcapsular cataract, Glaucoma  
- [Drug related] Scarring between conjunctiva and globe  
- Subdermal fat atrophy, Posterior uveitis, Increased predisposition to infections – herpes, fungal, Dermatitis, Delayed wound healing

**Complications related to injection:**

- Inadvertent intraocular injection  
- Retrobulbar hemorrhage  
- Subconjunctival hemorrhage

**2) Intravitreal Injection**

- Decreases growth factors  
- Stabilises endothelial cell tight junctions  
- Reduces permeability to water and solutes

Triamcinolone acetonide is the corticosteroid that has been shown to be useful in adjunctive therapy for uveitic CME, exudative ARMD, diabetic macular oedema and proliferative diabetic retinopathy

**Advantages of Intravitreal injection:**

- Controlled and consistent  
- More targeted delivery  
- Ability to bypass the blood / ocular barrier for the drug.  
- Immediate achievement of therapeutic ocular concentration  
- Reduced systemic toxicity  
- Eliminates long term side effects

**Dosage of IVTA** - 1 mg to 25 mg  
Commonest – 4 mg in 0.1 ml  
0.1 cc of 40 mg/ml (Kenalog) is injected into the vitreous cavity, 4 mm posterior to the limbus using ½ inch 30 gauge needle and a tuberculin syringe  
Following injection, indirect ophthalmoscopic examination, with special attention to patency of CRA is carried out.

**Additives in commercially available Triamcinolone acetonide** include

- Benzyl alcohol, Carboxy methyl cellulose and Polysorbate  
- 80.40 mg TA suspended in 0.1 ml vehicle contains 7.5 mg/ml sodium CMC, 0.4 mg/ml polysorbate 80, 9.25 mg/ml benzyl alcohol.

**Complications of Intravitreal injection:**

Injection related - localized SCH  
- Acute traumatic cataract
- RD due to increased vitreous traction or direct needle perforation of retina
- Vitreous hemorrhage
- Infectious endophthalmitis
- Non infectious endophthalmitis due to migration of drug into the anterior chamber
- Ocular hypertension
- Cataract

Guidelines for the use of prednisone in chronic ocular inflammation:
- Initial dose 1mg/kg/day
- Maximum adult oral dose 60 – 80 mg/day
- Maintenance dose (adult) = 10mg/day
- Tapering schedule 40mg/day, decrease by 10mg/day every 1-2 weeks
  - 20–10mg/day, decrease by 5mg/day every 1-2 weeks
  - 10-1 mg/day, decrease by 2.5mg/day every 1-4 weeks
- Monitor: Blood Pressure, Weight, Blood Glucose level every 3 months and annually. Measure bone density within first 3 months and annually thereafter.
- Supplementary treatment: Calcium 1500 mg daily and Vitamin D 800 IU daily. Estrogens as needed.
- In selected situations, where an immediate effect is needed, intravenous methylprednisolone can be started at a dose of 1gm/day x 3 days given as slow IV infusion and then start oral prednisone.
- Typically high dose oral corticosteroids are continued for no longer than one month. If the disease worsens or if there is no response after 2 – 4 weeks, an immunosuppressive agent should be added. Similarly if the disease is not completely quiet after 4 weeks of high dose oral prednisone, an immunosuppressive drug should be considered.
- Side effects of systemic steroid therapy are enumerated in Table 2.
- Taking into consideration all these effects, patients who require chronic oral corticosteroid therapy, especially at doses > 10mg/day, should be switched over to immunosuppressive agents.

C) Oral Corticosteroids

Oral corticosteroids are an effective therapy for the control of acute and chronic inflammation attendant to autoimmune diseases. With long term administration of these drugs, the adverse effects temper the overall effectiveness.

Systemic corticosteroids remain the initial drug of choice for most patients with bilateral endogenous sight threatening uveitis. Prednisone is the most commonly used oral corticosteroid, but for patients with serious liver dysfunction, prednisolone, the active form of prednisone is prescribed.

Intravitreal sustained drug delivery devices for steroid administration:

Fluocinolone, Dexamethasone, combination of Dexamethasone and Cyclosporine

Fluocinolone acetonide -
- is the steroid of choice for intravitreal injection
- it has a high potency similar to dexamethasone, a low solubility [1/24 of the solubility of dexamethasone] and being more lipophilic, it has more affinity to the posterior pole

Indications

i) Recalcitrant vision threatening noninfectious uveitis
ii) Unacceptable systemic side effects due to corticosteroids and immunosuppressive agents

Complications

- Intraoperative - mild vitreous hemorrhage
- Postoperative - hypotony, IOP rise, vitreous hemorrhage, dislocation of implant, retinal detachment, recurrence of uveitis

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Immunosuppressive Agents:

The potentially toxic newer immunosuppressive agents when administered in properly adjusted doses with careful monitoring, produce fewer adverse effects than chronic treatment with corticosteroids. They can be grouped as:

I Antimetabolites – Azathioprine and Methotrexate.
II Alkylating agents – Cyclophosphamide and Chlorambucil
III T Cell Inhibitors – Cyclosporine
Immunosuppressive drug regimen for initial therapy of ocular inflammation typically include high dose oral corticosteroids, since most of the above drugs take several weeks to have an effect. If the disease is quiet, in a patient who is on oral corticosteroid regimen, then the immunosuppressive drug is added at the appropriate dose and tapering of oral corticosteroids begun 4-8 weeks later. If the disease is active despite corticosteroid therapy then the patient is treated with high dose corticosteroids and the immunosuppressive drug. Immunosuppressive agents are given only in the absence of infection, when there is progressive visual loss and the disease is reversible.

I Antimetabolites

They competitively inhibit the utilization of normal substrates in nucleic acid synthesis.

1. Azathioprine: Is a purine nucleoside analogue. 
Mechanism of action: It interferes with DNA replication and RNA transcription. 
Indications: Chronic Uveitis, Behcets disease, Sarcoidosis 
Dose: 1-3 mg/kg/day 
Side effects: Bone marrow suppression

A complete blood count and platelet count should be done every 4 to 6 weeks in patients who are on azathioprine. Liver function tests should be performed every 12 weeks. When toxicity occurs (i.e., LFT > 1.5 times the upper limit of normal) dose should be decreased by 25-50 mg/day and the liver enzyme level re-evaluated after 2 weeks. The drug is stopped if total WBC<3000/mm$^3$ or platelet count <1,00,000/mm$^3$.

Tradename: Imuran, Azoran

2. Methotrexate: It is a folic acid analogue.
Mechanism of action: It inhibits dihydrofolate reductase which converts dihydrofolate to tetrahydrofolate. This inhibits synthesis of thymidilate which is essential for DNA replication.
Indications: Panuveitis, Intermediate uveitis, Vasculitis, Scleritis, Orbital pseudotumor 
Dose: 7.5 to 25 mg/week in a single dose (15 mg/week) Folate (1 mg/day) is administered concurrently to minimize nausea.

Side effects: Bone marrow suppression, hepatotoxicity, gastrointestinal-nausea, stomatitis, anorexia

Complete blood count and LFT to be done every 1 to 2 months.

Tradename: Mexitex, Oncotrex

II Alkylating Agents

Mechanism of action: The active metabolites alkylate...
purines in DNA and RNA resulting in cross linking which results in cell death. It decreases the number of activated T lymphocytes.

Indications: Severe bilateral sight threatening uveitis, Behcet’s disease, Intermediate uveitis, Scleritis, Wegener’s granulomatosis, Sympathetic ophthalmitis.

Dose:- 2mg/kg/day (starting dose – 150-200 mg/day)
The drug should be taken on empty stomach. The white blood cell count with differential must be monitored constantly beginning with a baseline value. Once there is a drop in the WBC count, the dosage may be decreased by 25-50 mg so that the count stabilizes at no lower than 3000/mm³. Intermittent cyclophosphamide therapy combined with steroid therapy yields long term failure rate in patients with Wegener’s granulomatosis. Adding systemic steroids permits lower dosage of both and thereby avoids some of the side effects of both drugs.

Side effects:- Bone marrow suppression, hemorrhagic cystitis (Monitor for microscopic hematuria once a month) teratogenicity, ovarian suppression, azoospermia.

Tradename: Cytoxan, Endoxan

(2) Chlorambucil

Mechanism of action: It is an alkylating agent. DNA to DNA cross linking and DNA to protein cross linking occurs which leads to interference in DNA replication, DNA transcription and nucleic acid function.

Indications: Behcet’s disease, Sympathetic Ophthalmitis
Patients typically require concomitant oral corticosteroids initially, and one goal of chlorambucil therapy is to taper and discontinue oral corticosteroids over a 2 month to 4 month period.

The typical duration of short term high dose treatment is 3-6 months.

Dose: 0.1 to 0.2 mg/kg/day.

Side effects
1. The primary side effect of chlorambucil is bone marrow suppression which is typically reversible.
2. Opportunistic infections, particularly viral infections. Prophylaxis for Pneumocystis carinii pneumonia should be considered.
4. Teratogenicity.

III Immunomodulators

Cyclosporine

Mechanism of action: Affects preferentially immuno competent T lymphocytes. Cyclosporine inhibits transcription in these cells blocking replication as well as their ability to produce lymphokines especially interleukin-2.

Indications:- Used as a steroid sparing agent in a wide variety of uveitis.

Dose:- 2-5 mg/kg/day in equally divided twice daily doses. Intravitreal sustained drug delivery devices which delivers the drug by diffusion mechanism has also been recently introduced.

Side effects:- The most serious and common side effect is nephrotoxicity (75%) Others include hypertension, hepatotoxicity, gingival hyperplasia, myalgia, tremor, paraesthesia, hypomagnesemia and hirsuitism. Monthly monitoring of blood pressure and serum creatinine levels are essential.

Tradename: Sandimmune, Neoral.

IV New Immunosuppressive Agents

1. Mycophenolate Mofetil:-

Mechanism of action :- It metabolizes to mycophenolic acid which reversibly inhibits inosine monophosphate dehydrogenase that inhibits guanosine nucleotide synthesis without incorporating into DNA. Its major effects are on T and B lymphocytes. This prevents lymphocyte proliferation, suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium and decreases recruitment of leucocytes to sites of inflammation.

The drug has high oral bioavailability but should be ingested on an empty stomach.

Indications: Mycophenolate mofetil has been reported to be effective in the prevention of allograft rejection in cases of renal and cardiac transplantation and multiple autoimmune diseases When compared to azathioprine, mycophenolate was associated with reduced rate of early graft failure.

Dose:- 2g/day (1g twice daily)

This should be used with caution in patients with renal impairment and in those with gastrointestinal disorders which might affect absorption.
Side effects: - Most common side effect – gastro intestinal effects, hepatotoxicity, bone marrow suppression.

Tradename: Cellcept

2. Tacrolimus: It is an immunomodulator.

Mechanism of action: It inhibits activation of T lymphocytes by inhibiting transcription in these cells.

Indications:
1. Tacrolimus is used for prevention and treatment of organ transplant rejection.
2. The main use for ocular illness is in infectious uveitis.

Dose: Initial dose of 0.05 mg/kg/day

Monitoring of blood counts is necessary.

Side effects: - Major side effects include
1. Renal impairment (28%)
2. Neurologic symptoms (21%)
3. Gastro intestinal symptoms (19%)
4. Hyperglycemia (13%)

Others – hypomagnesemia, tremor, headache, paraesthesia and hypertension.

Tacrolimus should not be given with cyclosporine because of the similar risks of renal toxicity. Patients should undergo weekly laboratory assessment of the following: liver enzymes, bilirubin, blood urea nitrogen, creatinine, electrolytes including calcium, magnesium and phosphate, glucose and complete blood counts at least initially. With stable dosing the frequency may be reduced monthly.

Tradename: FK 506

3. Daclizumab

Mechanism of action: - The IL-2 receptor system is a well characterized lymphokine receptor system that plays a central role in the induction of immune responses. Daclizumab builds to the alpha chain of IL-2 receptor and blocks the IL-2 mediated responses.

Indication: Non infectious uveitis

Dose: 1 mg/kg two weekly

Side effects:
Cutaneous lesions, Upper respiratory infections, Bronchitis, Herpes zoster infections.

4. Etanercept: It contains 2 identical soluble tumor necrosis factor receptors (TNF) that have been fused with IgG Fc fragment. This molecule binds to and inactivates TNF.

Indication: Rheumatologic disorders – Adult and juvenile rheumatoid arthritis.

Dose: 25 mg subcutaneously twice weekly.

Side effects: -
1. The major side effect is infection (including sepsis) (35%)
2. Most frequent side effect was injection site reactions (37%)
3. Others – headaches (17%) rarely – malignancies

Tradename: Enbrel

5. Infliximab: It is a chimeric monoclonal antibody directed against tumor necrosis factor – alpha. It interferes with the binding of TNF to the receptors. TNF – α enhances leucocyte migration and activates the proinflammatory cytokines like interleukin-1 and interleukin – 6. Infliximab by interfering with the binding of TNF to the receptors, decreases proinflammatory cytokines.

Indications
HLA B 27 associated anterior uveitis, Behcet’s disease

Dose: 5mg/kg

1st dose on the first day of therapy
2nd dose at the end of 2 weeks &
3rd dose at the end of 6 weeks

Infliximab is available as 100 mg lyophilized powder which has to be reconstituted with 10 ml sterile water.

Side effects: -
1. Major side effect is increased risk of infections, particularly tuberculosis and histoplasmosis capsulatum, aseptic meningitis.
2. The use of infliximab may enhance brain lesions associated with multiple sclerosis.
3. Autoimmunity – Lupus like syndromes
4. Rarely malignancies

Tradename: Remicade

6. Oral retinal S antigen: Oral tolerance is an approach that has received much clinical interest recently.

Indications: - Pars planitis, Behcet's disease, Multiple sclerosis, Rheumatoid arthritis

Dose: 30 mg of S antigen 3 times a week. No specific significant toxic effects attributable to S antigen therapy has been reported.
Patients on immunosuppressive therapy require strict, periodic follow up with periodic complete blood counts, liver function tests, renal function tests etc.

References

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