ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Commentary

Updates in Medical Management of Uveitis

Mohamed Salem*

Clinical Lecturer of Gulf medical university, UAE

***Corresponding Author:** Mohamed Salem, Clinical Lecturer of Gulf medical university, UAE.

Received: April 18, 2019; **Published:** May 30, 2019

Different agents can be used separately or concomitantly according to the severity and type of the inflammation.

Mydriatic and cycloplegic drugs

Mechanism of action:

- Breaking or preventing the formation of posterior synechiae.
- Relieving photophobia secondary to ciliary spasm.

Dose and frequency: The stronger the inflammatory reaction, the stronger or more frequent the dosage of the cycloplegic drug.

Types:

- Short-acting drops such as cyclopentolate hydrochloride, 1%,
- Long-acting drops such as atropine may be used.

Why short acting drugs are preferred?

They allow the pupil to remain mobile with rapid recovery (6 - 12 hours) when discontinued.

Nonsteroidal anti-inflammatory drugs

Mechanism of action

Inhibiting cyclooxygenase (COX) isoforms1 and 2, or 2 alone, and they reduce the synthesis of prostaglandins that mediate inflammation.

COX isoforms:

- COX-1is present in nearly all cells and appears to be involved in cellular metabolic events such as gastric cytoprotection, platelet aggregation, and renal function.
- COX-2 seems to mediate inflammation.

Why selective COX-2 inhibitors are preferred?

They reduce the risk of secondary gastrointestinal damage compared with nonselective COX inhibitors but they have more adverse effects and some have been withdrawn from the market such as rofecoxib, valdecoxib and Celecoxib.

Potential complications of prolonged systemic NSAID use:

1. Myocardial infarction;
2. Hypertension, and stroke (especially with selective cox-2 inhibitors);
3. Gastric ulceration;

4. Gastrointestinal bleeding;
5. Nephrotoxicity; and
6. Hepatotoxicity.

NB. Ketorolac, bromfenac and nepafenac may be used for the treatment of CME.

Severe corneal complications such as keratitis and perforation are expected to be seen with prolonged use of topical NSAIDs but records are very rare and confined to the generic derivatives of diclofenac which is nearly obsolete and related to some vulnerable cases such as dry eye and rheumatoid arthritis.

Corticosteroid

The mainstay of treatment, however it is preserved for the following situations because of their potential complications:

- Treatment of active inflammation in the eye,
- Prevention or treatment of complications such as cme,
- Reduction of inflammatory infiltration of the retina, choroid, or optic nerve.

NB: Corticosteroids must be tapered gradually (over days to weeks) and not stopped abruptly if utilized for longer than 2 - 3 weeks to prevent cortisol deficiency resulting from hypothalamic-pituitary-adrenal (HPA) axis suppression.

NB: If surgical intervention to treat uveitis or its complications is required; the dosage may need to be increased to prevent postoperative exacerbation of the uveitis.

Modes of administration of steroids in treatment of uveitis

Topical administration:

- Mainly used for anterior uveitis although it can be used to control vitritis or macular odema in some eyes.
- Difluprednate 0.05 % (8 folds higher than prednisolone acetate 1%).
- Difluprednate 0.05% has the same adverse effect like Prednisolone acetate 1% with particularly higher effect on the IOP rise during therapy.
- Rimexolone, loteprednol, and fluorometholone produce a smaller ocular hypertensive effect than that of other medications however these drugs have less inflammatory comparable to prednisolone acetate 1% so they can be preserved for the mild to moderate conditions of anterior uveitis.

Periocular administration:

- Indicated for patients with intermediate or posterior uveitis or CME.
- Periocular corticosteroids can cause systemic adverse effects similar to those of oral corticosteroids.
- Triamcinolone acetonide (40 mg) and methylprednisolone acetate (40 - 80 mg) are the most commonly used drugs.
- Periocular injections can be performed using either a transseptal or a sub-Tenon (Nozik technique) approach with a sub-Tenon injection, a 25-gauge, ⅝-inch needle is used in the original description by Nozik.

NB1: Periocular injections should not be used in cases of infectious uveitis (e.g. toxoplasmosis) and should be avoided in patients with necrotizing scleritis because scleral thinning and perforation may result.

NB2: The physician should be aware that periocular corticosteroid injections have the potential to raise the IOP precipitously or for a long time, particularly with the longer-acting drugs (triamcinolone or methylprednisolone). If this effect occurs, the periocular steroid should be removed surgically, especially if it had been given anterior to the septum or in a subconjunctival space.

NB3: Subconjunctival administration is generally not performed because of the risk of subconjunctival migration of the steroid vehicle.

Intravitreal administration:

Intravitreal triamcinolone acetonide

- 4 mg/0.1 mL Single trans-pars plana intravitreal injections of triamcinolone may produce sustained visual acuity improvements for 3-6 months in non-vitrectomized eyes.
- CME may recur after 3 - 6 months.
- Repeated injections increase the risk of cataract formation and IOP elevation.
- FDA approved preservative free Triamcinolone acetonide is recommended to avoid development of sterile endophthalmitis.

The sustained-release fluocinolone implant

- 0.59-mg implant is effective for a median of 30 months, with a mean time of 3 years to the first recurrence.
- Well control of intraocular inflammatory reaction requires nearly a year with minimum recurrence rate.
- Complications such as cataract and IOP elevation is reported in most cases.
- Other complications such as infectious endophthalmitis, hypotony, wound leaks; vitreous hemorrhage and retinal detachment are also reported.

Dexamethasone implant

- A biodegradable intraocular implant containing 700 μg of dexamethasone approved by the FDA and in Europe for the treatment of uveitis affecting the posterior segment of the eye and retinal vein occlusion.
- Injected through a pars plana approach to the vitreous cavity.
- Relative contraindications to using this implant are aphakia, vitrectomy, and having a decentered intraocular lens because of the risk of implant migration into the anterior chamber.

Systemic administration:

- Most patients require 1 - 2 mg/kg/day of oral prednisone, usually no higher than 60 - 80 mg daily.
- Gradually tapered every 1 - 2 weeks.
- Treatment with corticosteroids may last for 3 months or, in some cases, longer so the IMT may be indicated to avoid complications of corticosteroid.
- In cases of an explosive onset of severe noninfectious posterior uveitis or pan uveitis, therapy with intravenous, high-dose, pulse methylprednisolone (1 g/day infused over 1 hour) may be administered for 3 days, followed by a gradual taper of oral prednisone starting at 1 - 1.5 mg/kg/day.
- Adverse effects are numerous and can be life-threatening (hypertension, elevated glucose level and psychological disturbances).

NB.1: Patients with the following diseases are at a particular high risk of corticosteroid induced exacerbation of their conditions:

1. Peptic ulcer,

2. DM,
3. Hypertension,
4. GERD,
5. Psychiatric conditions,
6. Immunocompromised.

NB.2: Caution in prescription of concomitant corticosteroid and NSAID as it increases the risk of developing or exacerbating of gastric ulcers (H2 blockers are recommended).

NB.3: Calcium and VitD levels should be monitored carefully to avoid osteoporosis.

The following tests may be used to evaluate patients at risk for corticosteroid-induced bone loss:

- Serial height measurements.
- Serum calcium and phosphorus levels.
- Serum 25-hydroxycholecalciferol levels (if vitamin d stores are uncertain).
- Fsh and testosterone levels (if gonadal status is uncertain).
- Bone-mineral-density screening (for anyone receiving corticosteroid therapy for more than 3 months).

Immunomedulatory medications

These drugs should also be considered in patients who require long-term corticosteroid therapy (longer than 3 months) at doses greater than 5 - 10 mg/day

Indications

The use of IMT in uveitis is warranted for consideration in the following settings:

- Vision-threatening intraocular inflammation.
- Disease process that is likely reversible inadequate response to corticosteroid treatment.
- Failure of therapy.
- Corticosteroids contraindicated because of systemic problems or intolerable adverse effects.
- Unacceptable corticosteroid adverse effects.
- Long-term corticosteroid dependence.

**Some conditions may respond initially to corticosteroid but with IMT has been shown to improve long-term prognosis and lessen visual morbidity such as:

- Ocular cicatricial pemphigoid,
- Serpiginous choroiditis,
- Behçet disease,
- Sympathetic ophthalmia,
- VKH syndrome,
- Necrotizing scleritis associated with systemic vasculitis.

Treatment

Before initiating IMT, the physician should ensure that there is:

- An absence of infection.
- An absence of hepatic and hematologic contraindications.
- Meticulous follow-up available from a physician who is, by virtue of training and experience.
- Qualified to prescribe and safely monitor such medications and personally manage their potential toxicities.
- Objective longitudinal evaluation of the disease process.
- Informed consent.

Several classes of immunomodulatory medications exist:

1. Antimetabolites,
2. Inhibitors of T-cell signaling,
3. Alkylating agents,
4. Biologic response modifiers.

NB: There may be a delay in therapeutic response for weeks to months after initiation of IMT; therefore, corticosteroids are required to be continued until the IMT agent initiates its effect the time when steroid should be tapered.

Serious complications include:

- Renal and hepatic toxicity, bone marrow suppression.
- Increased susceptibility to infection.
- Alkylating agents may cause sterility and an increased risk of future malignancies such as leukemia or lymphoma.
- All of these medications are potentially teratogenic, and women should be advised to avoid becoming pregnant while taking them.

Antimetabolites

Azathioprine

- **Nature and action:** A purine nucleoside analogue interfere with DNA replication and RNA transcription.
- **Recommended dose:** Up to 2 mg/kg/day orally in adults.
- **Indications:** It is shown to be effective in:
- Behçet disease.
- intermediate uveitis.
- VKH syndrome.
- sympathetic ophthalmia.
- Necrotizing scleritis.

Adverse effects and complications:

- Bone marrow suppression (concomitant Allopurinol will increase the risk).
- Reversible hepatotoxicity.

Thiopurine S-methyltransferase (TPMT):

- An enzyme responsible for the metabolism of 6-mercaptopurine (6-MP).
- A genotypic test is available that can help determine patient candidacy for azathioprine therapy before treatment and can help clinicians individualize patient doses.

Evaluation of TPMT activity has revealed 3 groups of patients:

- **Low/no TPMT activity:** Azathioprine therapy not recommended.
- **Intermediate TPMT activity:** Azathioprine therapy at reduced dosage.
- **Normal/high TPMT activity:** Azathioprine therapy at higher doses than in patients with intermediate TPMT activity.

Methotrexate

Nature and action: Is a folic acid analogue and inhibitor of dihydrofolate reductase; it inhibits DNA replication, but its anti-inflammatory effects result from extracellular release of adenosine.

Indications:

- JIA associated anterior uveitis,
- Sarcoidosis, panuveitis,
- Scleritis.

Dose: Usually starting at 10 - 15 mg/week and gradually increasing to a maintenance dose of 15 - 25 mg/week in adults.

- Methotrexate can be given orally, subcutaneously, intramuscularly, or Intravenously and is usually well tolerated.
- Folate is given concurrently at a dose of 1 mg/day to reduce adverse effects.
- Methotrexate may take up to 6 months to produce its full effect in controlling intraocular inflammation.

Adverse effects:

- Gastrointestinal distress and anorexia,
- Reversible hepatotoxicity,
- Cirrhosis,
- Teratogenic.

NB1: Methotrexate is the first-line choice for IMT in children.

NB2: Recently, intravitreal injections of methotrexate (400 µg) for the treatment of refractory uveitis and uveitic CME.

Mycophenolate mofetil

- **Mechanism of action:** Inhibits both inosine monophosphate dehydrogenase and DNA replication.
- **Dose:** 1 - 1.5g twice daily in adults.
- **Adverse effects:** Reversible gastrointestinal distress and diarrhea.
- **Indications:** An effective corticosteroid-sparing agent in up to 85% of patients with chronic uveitis. It has similar efficacy in children (88%) and can be a safe alternative to methotrexate in patients with pediatric uveitis.

Inhibitors of T-cell signaling:

Agents that inhibit T-cell signaling include:

1. Cyclosporine,
2. Tacrolimus,
3. sirolimus.

Nature and action:

- **Cyclosporine:** A macrolide product of the fungus *Beauveria nivea.*
- **Tacrolimus:** a product of *Streptomyces tsukubaensis*, are calcineurin inhibitors that eliminate T-cell receptor signal transduction and downregulate interleukin-2 (IL-2) gene transcription and receptor expression of CD4+ T lymphocytes.
- **Sirolimus:** an antifungal product of *Streptomyces hygroscopicus*, is a non-calcineurin inhibitor of T-cell signaling that inhibits antibody production and B lymphocytes.

Dose of cyclosporine: 1 - 5 mg/kg/day (oral preparations).

Dose of tacrolimus: 0.10 - 0.15 mg/kg/day in adults.

The most common adverse effects:

1. Systemic hypertension,
2. Nephrotoxicity,
3. Paresthesia,
4. Gastrointestinal upset,
5. Fatigue,
6. Hypertrichosis, and
7. Gingival hyperplasia.

Monitoring:

- Blood pressure, serum creatinine levels, and complete blood counts must be assessed regularly.
- If serum creatinine level rises by 30%, dose adjustment is required.
- Sustained elevation of serum creatinine levels will require a cessation of medication until levels return to baseline.
- It is usually not necessary to monitor drug levels unless there is a concern about patient adherence or drug absorption.
- Patients with psoriasis treated with cyclosporine appear to be at greater risk of primary skin cancers.

Indications:

- Behçet uveitis,
- intermediate uveitis,
- posterior uveitis, including VKH syndrome.

NB: Tacrolimus is shown to have less nephrotoxicity and elevated blood pressure than cyclosporine.

Alkylating agents

They include cyclophosphamide and chlorambucil.

- Used only if other immunomodulators fail to control uveitis
- Used as first-line therapy for necrotizing scleritis associated with systemic vasculitides such as granulomatosis with polyangiitis.
- The most worrisome adverse effect is an increased risk of malignancy such as leukemia and bladder cancer

Cyclophosphamide:

- An alkylating agent whose active metabolites alkylate purines in DNA and RNA, resulting in impaired DNA replication and cell death.
- Cytotoxic to resting and actively dividing lymphocytes.
- It is absorbed orally and metabolized in the liver into its active metabolites.
- Dose: 2 mg/kg/day in adults.
- Myelosuppression and hemorrhagic cystitis are the most common adverse effects.
- Hemorrhagic cystitis is more common when cyclophosphamide is administered orally.
- Other toxicities include teratogenicity, sterility, and reversible alopecia.
- Opportunistic infections such as Pneumocystis jirovecii pneumonia occur more commonly in patients receiving cyclophosphamide (trimethoprim-sulfamethoxazole prophylaxis is recommended).
- Cyclophosphamide has been shown to be effective in treating necrotizing scleritis.

Chlorambucil:

- Is a very long-acting alkylating agent that also interferes with DNA replication.
- Dose: 0.1-0.2 mg/kg in adults (well absorbed orally).
- it is myelosuppressive therefore complete blood counts should be monitored closely.
- It is also teratogenic and causes sterility.
- Indicated in cases of sympathetic ophthalmia, Behçet disease, and other sight-threatening uveitic syndromes.

Biologic response modifiers

Nature and action:

- Inflammation is driven by a complex series of cell-cell and cell-cytokine interactions.
- Inhibitors of various cytokines have been labeled biologic response modifiers.
- Infliximab and Adalimumab are biologics that inhibit the action of tumor necrosis factor α (TNF-α) which is believed to play a major role in the pathogenesis of JIA, ankylosing spondylitis, and other spondyloarthropathies.

Infliximab

- A chimeric, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody directed against TNF-α, is effective in controlling current inflammation and guard against the future attacks in Behçet uveitis, idiopathic uveitis, sarcoidosis, VKH syndrome and HLA-B27-associated anterior uveitis.

- It is administered through infusions.
- Adverse effects and toxicity including drug-induced lupus, systemic vascular thrombosis, congestive heart failure, new malignancy, demyelinating disease, and vitreous hemorrhage.
- Low-dose methotrexate (5 - 7.5 mg/week) may be administered concomitantly to reduce the risk of drug-induced lupus syndrome.
- PPD test or interferon-gamma release assay to assess for tuberculosis (TB) exposure is mandatory before starting infliximab to prevent disseminated TB that may develop after initiating the infliximab for post-primary tuberculosis even if inactive.

Adalimumab

- A fully human monoclonal IgG1 antibody directed against TNF-α, has been shown to be as effective as infliximab particularly in pediatric uveitis.
- Adalimumab is less expensive than infliximab and can be self-administered by subcutaneous injection every 2 weeks, without the need for the intravenous infusions required by infliximab.

Rituximab

A chimeric monoclonal antibody directed against CD20+ cells (mainly B lymphocytes) may also be useful in the treatment of Behçet retinal vasculitis, granulomatosis with polyangiitis- associated necrotizing scleritis, and mucous membrane pemphigoid.

Anakinra

Is a recombinant IL-1 receptor antagonist that holds some promise as a biologic treatment alternative for JIA-associated uveitis. It also successfully treats neonatal-onset multisystem inflammatory disease (NOMID), which can cause uveitis.

Tocilizumab

Is a humanized monoclonal antibody against the IL-6 receptor. There are case reports of successful treatment of JIA-associated uveitis and other types of uveitis that have been refractory to other treatments.

Intravenous immunoglobulin (IVIG)

Effective in treating refractory uveitis and in patients with mucous membrane pemphigoid.

Interferon alfa-2a/2b (IFN-α2a/b)

- Alternative to anti-TNF drugs.
- It has antiviral, immunomodulatory, and antiangiogenic effects.

Indications:

- Behçet uveitis (90% cure rate),
- Non-Behçet uveitis (60% cure rate),
- Uveitic CME.

Adverse effects:

- Leukopenia or thrombocytopenia may occur despite dose lowering.
- Depression.

Volume 10 Issue 6 June 2019