Non-steroidal immunosuppressive drugs for non-neoplastic ocular disorders

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Introduction

Immunomodulatory or immunosuppressive drugs have an ability to suppress the immune drive by producing certain soluble bioactive molecules like cytokines and chemokines thus decreasing the tissue damage resulting from the inflammatory mediators. The use of immunosuppressives in ophthalmology follow their extensive use as anticancer chemotherapeutic agents. Non- neoplastic use of immunosuppressive agents by ophthalmologists has greatly increased over the past three decades because of better knowledge of the immunopathology of immune mediated, non-infectious ocular inflammatory disorders, affecting conjunctiva, cornea, sclera, uveal tissue etc.[1]. Most of the uveal disorders such as non-infectious uveitis associated with arthritis and collagen vascular diseases e.g. Vogt-koyanagi-Haradas disease, Behecet's disease, sympathetic ophthalmitis, pars planitis etc are immune mediated and require immunosuppressive agents if corticosteroids fail or are not tolerated or contraindicated.

Allergic eye diseases like vernal keratoconjunctivitis and atopic keratoconjunctivitis are characterized by complex immunopathology. Immunomodulating agents like cyclosporine A and tacrolimus can be used to inhibit T-cell activation among the patients with severe allergic eye diseases[2]. Other immune mediated ocular conditions which require immunosuppressive drugs are thyroid associated ophthalmopathy (TAO), dry eye disease, necrotizing scleritis, moorener's ulcer, limbal cell transplantation and peripheral ulcerative keratitis (PUK).

Earlier, the use of immunosuppressives were limited to treatment of corticosteroid resistant, sight threatening ocular inflammation , but now a days these drugs are considered as first line of treatment for Wegeners granulomatosis, Behcets's disease etc. Most of the immunosuppressive agents are extremely potent and have significant adverse effects[3].

The purpose of this review is to briefly summarize the management of various ocular inflammatory disorders by using immunosuppressive agents, with focus on use of newer immunosuppressive drugs. A review of the literature in the PubMed, MedLine, and Cochrane database was conducted to identify clinical trials, comparative studies, case series and case reports describing the use of immunosuppressive therapy.

Immunosuppressive Drugs

The potentially toxic newer immunosuppressive agents when administered in properly adjusted dose with careful monitoring, produce fewer adverse effects than chronic treatment with corticosteroids.

According to relative selectivity, immunosuppressive drugs are categorized as Category 1-Highly nonspecific, effect on all proliferating cells e.g. anti-metabolites and alkylating drugs. Category 2 - It eradicates only the immunocompetent cells. Category 3- More selective drug, effects only a sub-population of lymphocytes e.g.; cyclosporine. Category 4-Highly specific drugs, effects antigen specific cell population.

According to mechanism of action immunosuppressive can be grouped into:

1. Antimetabolites: Azathioprine and Methotrexate.
2. Alkylating agents: Cyclophosphamide and chlorambucil.
3. T-cell Inhibitors: Cyclosporine.
4. Few newer Agent

Antimetabolites

They competitively inhibit the utilization of normal substrates in nucleic acid. These include: Purine analogues such as azathioprine and mercaptopurine, Folic acid analogues such as methotrexate, Pyrimidine analogues such as fluorouracil Protein synthesis inhibitors.

Azathioprine: Azathioprine is a purine analog and pro-drug of 6-mercaptopurine, that is converted to thioinosine 5-phosphate which serves as purine analog and interferes with DNA replication and RNA transcription[4]. Its effect is dose dependent and highly nonspecific and effects on all proliferating cells. It

inhibits T lymphocyte function and suppresses the type IV hypersensitivity reaction and interferes with the participation of natural killer cells (NK) in antigen dependent cytotoxic reaction. SITE study included 145 patients treated with azathioprine out of which 47% of them experienced steroid sparing effect[5,6].

Drug is indicated in Chronic Uveitis, Systemic Lupus Erythematosis, Behcet's disease, Sarcoidosis etc. 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.

Recommended dose in ocular diseases is 1-3 mg/kg/day and most common side effects are myelosuppression and hepatotoxicity. 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 are-evaluated after 2 weeks. The drug is stopped if totalWBC<3000/mm3 or platelet count <1,00,000/mm3[7].

Methotrexate(MTX): Methotrexate is a folic acid analogue. It inhibits DNA replication by inhibiting enzyme dihydrofolatereductase which converts dihydrofolate to tetrahydrofolate. This inhibits synthesis of thymidilate which is essential for DNA replication[8]. It reduces cellular and humoral response by affecting proliferation, inducing T-cell apoptosis, inhibiting cytokine production and angiogenesis.

Methotrexate is indicated in panuveitis, Intermediate uveitis, vasculitis, rheumatoid scleritis, orbital pseudo-tumor, myosits and sarcoidosis associated panuveitis[10-12]. MTX is used as first choice in paediatric uveitis with juvenile rheumatoid arthritis[9]. 6 MTX a good option as primary treatment or steroid sparing agent.

The systemic immunosuppressive therapy for eye diseases (SITE), multi-center retrospective cohort study of 384 patients treated with methotrexate as the only immunosuppressant for ocular inflammation showed that 66% of patients were able to achieve quiescence of their ocular inflammation within a year[13]. Doses are 7.5 to 25 mg/week in a single dose (15 mg/week) Folate (1mg/day) is administered concurrently to minimize nausea[14] .

Common side effects are bone marrow suppression, hepatotoxicity, gastrointestinal toxicities like -nausea, stomatitis, anorexia. Complete blood count and LFT to be done every 1 to2 months.

ll-Alkylating agents: The alkylating agents used in immunotherapy are nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds and others. Cyclophosphamide (Baxter's Cytoxan) is probably the most potent immunosuppressive compound.

Cyclophosphamide

Cyclophosphamide, also known as Cytoxan, which induces cross-linking of cellular nucleic acid resulting in aberrant base pairing, cleavage of DNA stand and ultimately termination of cell cycle and cell death[14]. It has cytotoxic effect on rapidly proliferating cells such as cancer cells and immunocompetent T and B-lymphocytes[16]. Cyclophosphamide has been tried in severe sight threatening intermediate uveitis, scleritis, sympathetic ophthalmia and Behcet's disease. Its most common use is in oncology as an anti-cancer agent, for which it is approved by the US Food and Drug Administration. It is used in several autoimmune disease, the most common being systemic lupus erythematosis and vascuitis, particularly Wegner's granulomatosis[17-22].

The recommended daily dose for ocular use is 1-2mg/kg day. The drug is available in parenteral and oral preparations but oral route is preferred. It has been avoided in pregnancy and lactating mothers. Important side effects of Cyclophosphamide include leukopenia, sterility, hemorrhagic cystitis/ hematuria and risk of opportunistic infections and carcinoma. It can cause dry eyes and raised intraocular pressure.

Chlorambucil

Chlorambucil is another nitrogen mustard similar to Cyclophosphamide. It is slow acting and least toxic but highly carcinogenic nitrogen mustered. Like other ankylating agent, it replaces hydrogen ions with alkyl groups on nitrogen base and interferes with DNA replication, transcription and nucleic acid function due to DNA to DNA and DNA to protein cross linking[23].

Drug has been used in the treatment of Behcet's disease, sympathetic ophthalmia, Crohn's disease and non- infectious HLA-B27 related uveitis. Maximum studies published with chlorambucil are in Behcet's disease[24-28]. It also used in many malignancies, including leukemia, Non-Hodgkins lymphoma, Hodgkin disease etc. It has been used in rheumatic diseases, but less frequently than cyclophosphamide[23].

Oral administration is the preferred route, drug is started after getting baseline CBC and LFT tests done. The initial dose is of 2mg/day then increased to 2mg/day every week until inflammation completely resolved. Maximum dose must not exceed 18mg/day. Most serious side effects of Chlorambucil is myelosuppression. Other effects are sterility, alopecia, pulmonary fibrosis and seizures.

Drugs Acting on Immunophilins

Cyclosporine

Cyclosporine A (CsA) is a potent immunosuprresive drug, was first isolated in 1970 as fungal anti-metabolite from fungus *Tolypocladium*

infantum. Primarly used in organ transplantation and autoimmune diseases. It acts by binding tocyclophilin/ immunophilin, acytosolic protein of T lymphocyte and this complex then inhibits calcineurin (calcium-calmodulin dependent phosphoprotein phosphatase), which in turn inhibits the transcription factor required for the expression of cytokine genes. Thus Cyclosporine inhibits T helper cell activation and production of interleukin (IL)[2,3,4] tumor necrosis factor (TNF) and gamma interferon[5].

Cs A has been used as steroid sparing agent in a variety of uveitis. Several studies have reported its usefulness in Behcet's disease, Vogt–Koyanagi–Harada and sarcoidosis[29]. In a low concentration (0.05% - 0.1%) topical Cs A is effective in patients with vernal keratoconjunctivitis, atopic keratoconjunctivitis and dry eye syndrome.

The SITE study evaluated 373 patients with ocular inflammation treated with CsA in which 52% of them were able to achieve inflammation control and tapering of systemic steroids was achieved in 36% of patients at the 1-year time point. About 10.7% of patients stopped therapy within a year due to toxicity. About 55 patients discontinued CsA after 1 year of therapy due to remission.

CsA is available for oral use as a white crystalline powder dissolved in oil base. Drug is metabolized in liver and excreted in bile. The recommended dose is 2-5mg/kg/day in equally divided twice daily dose. Recently an intravitreal sustained drug delivery device has also been introduced.

The most common side effects of oral CsA are nephrotoxicity, hypertension, hepatotoxicity, gingival hyperplasia, revercible myopathy and hirsutism etc. The above toxicities are dose dependent. No adverse reaction has been reported with topical cyclosporine except for mild and transient burning sensations upon administration of moderate to high concentration of topical CsA.

Voclosporin

Voclosporin, (luveniq) is another calcineurin inhibitor that affects T helper cells (TH) 1 and TH17-mediated responces. It is a more potent inhibitor of T helper lymphocytethan cyclosporine and having a more predictable pharmacokinetic profile.[31-32] The Lux Uveitis Multicenter Investigation of a New Approach to Treatment (LUMINATE) trial demonstrated superiority to placebo in reducing vitreous haze and a 50% decrease in the recurrence rate of inflammation at 6 months with tolerable side effects[33,34].

Voclosporin was dosed orally at 0.4 mg/kg twice a day. However, the primary end point for the phase 3 clinical trials to show reduction in vitreous haze at week 12 or at the time of treatment failure, was not achieved and Lux Biosciences Inc. (NJ, USA) ended its plans to proceed with the drug development for uveitis.

Newer Immunosuppressive Agents

1) **Mycophenolate Mofetil (MMF):** It metabolizes to active molecules mycophenolic acid which inhibits guanosine nucleotide synthesis without incorporating into DNA by inhibiting the enzyme inosine monophosphate dehydrogenase. It prevents lymphocyte proliferation, antibody synthesis and with cell adhesion on vascular endothelium. It has been reported to be effective in cases of renal and cardiac transplantation to prevent allograft rejection. Drug is often used as a corticosteroid sparing agent in chronic inflammatory eye disease such as sympathetic ophthalmia, Behcet's disease, Vogt-Koyanagi-Harada syndrome, serpiginous choroiditis. The recommended daily dose of MMF is 500 mg twice a day, orally on empty stomach and increased to 1gm twice a day with maximum dose of 3gm a day. The most common side effect is gastrointestinal irritability, followed by bone myelosuppression and hepatotoxicity.

2) **Tracrolimus:** Tacrolimus (earlier known as FK-506) is a macrolide lactone derived from bacterium *Streptomyces tsukubaensis*. Its mechanism of action is similar to cyclosporine but it is more potent than cyclosporine and has less pronounced side-effects. Tacrolimus interferes with the calcineurine phosphatase pathway which regulates T-cell mediated immune response. Tacrolimus inhibits activation of T-Lymphocytes, T-helper cell mediated B-cell proliferation and inhibiting release of mediators of mast cell. It has been reported that tacrolimus has ability to resolve giant papillae due to vernal keratoconjuctivitis (VKC) and atopic keratoconjuctitis (AKC). This drug has been used in Sjogren's syndrome, atopic dermatitis and hepatic, renal & bone marrow transplantation for prevention and treatment of transplant rejection.

Initial dose of systemic drug is 0.05mg/kg/day but in infectious uveitis and allergic eye diseases, tracrolimus is commonly used in topical formulations, mainly at concentration of 0.03 – 0.1%.

Major side effects include renal impairment, neurologic symptoms including paraesthesia& tremor gastrointestinal symptoms, hyperglycemia, hypomagnesemia, and hypertension. Hence one has to monitor complete blood count, blood urea nitrogen, serum creatinine, liver enzymes and serum electrolytes. Tacrolimus should not be given with cyclosporine as it also causes renal toxicity[35].

3) **Daclizumab:** It is a humanized monoclonal antibody directed against the interleukin (IL)-2 receptor of activated lymphocytes. Daclizumab specifically builds to the alpha chain of IL-2 receptor and blocks the IL-2 mediated cytokine responses. It affects only the T-lymphocyte

response and have no impact on the humoral immunity.

Daclizumab has been used in treating childhood uveitis, non-infectious intermediate and posterior uveitis and birdshot retinochoroidopathy[33,36-40]. Drug is administered intravenously 1–4 mg/kg every 14 days. Although drug is usually well tolerated but patient may have side effects like headache, nausea, lymphadenopathy and skin lesions, herpes zoster and respiratory infection. Studies done on patients receiving daclizumab for transplants did not show an increased risk of malignancy or mortality[41,42].

4. Etanercept

It is a bivalent, soluble receptor for tumor necrosis factor (TNF). It competitively binds TNF-α and TNF - β and inactivates TNF resulting into decreased synthesis of pro-inflammatory cytokines (IL-1 & IL-6), matrix metalloproteinase and leukocyte migration.

Etanercept has been effective in the treatment of rheumatoid arthritis, but its effect in uveitis is debatable[33,43,44]. Study showed some improvement with etanercept in Behcet's associated uveitis and pediatric patients[45]. The SITE study showed an increased risk of cancer-related mortality in patients taking TNF inhibitors, including etanercept[45]. Drug is administered via a subcutaneous route, 25 mg twice a week for a period of 2 years. The most common side effect is pain and sepsis at the site of injection. Anti-TNF therapy is contraindicated for patients with active systemic infection and severe heart failure.

5. **Adalimumab**

It is a human immunoglobulin(Ig) G1 monoclonal anti-TNF-α antibody, specifically target cytokines or their inflammatory signaling pathways. Drug is indicated for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and juvenile idiopathic arthritis.

It reduces flares of uveitis in the pediatric populations and in patients with juvenile idiopathic arthritis, and in patients with spondyloarthropathy-associated uveitis[47-51].

It is administered via subcutaneous injection in doses of 40 mg given at 2-week intervals. It can be used in conjunction with other immunomodulator agents such as methotrexate and mycophenolat mofetil in order to achieve remission. The common side effects of adalimumab include pain at the site of injection, upper respiratory, sinus and urinary tract infections, gastrointestinal discomfort, elevated cholesterol and high blood pressure.

6. lnfliximab

It is a chimeric IgG monoclonal antibody, directed against TNF-α. It interferes with the binding of TNF to the receptors, decreasing pro-inflammatory cytokines. Drug is indicated in autoimmune disorders like psoriasis, rheumatoid arthritis and crohn's disease and also in treating ocular complications of Behcet's disease not controlled by any means and refractory uveitis in patients with juvenile idiopathic arthritis[51-55].

Infliximab has been associated with anaphylactic reactions, demyelinating disease and heart failure and should be used with caution in patients with a known past medical history that may be affected by potential side effects[56].

It is proposed that TNF inhibitors do not initiate cancer but exacerbate pre-existing malignancies that are undetected[33,46,57]. Infliximab is administered as an intravenous infusion at 5mg/kg at week 0 and 2 as loading/doses followed by infusions at 4-week intervals. For refractory cases, the doses can be as high as10 mg/kg. The dosing can be increased or tapered and the dosing intervals can be adjusted based on clinical response and state of inflammation.

Major side effect is increased risk of infections such as tuberculosis, histoplasmosism and aseptic meningitis[58]. It can enhance brain lesions associated with multiple sclerosis and Lupus like syndromes

7. 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. The recommended dose is 100mg four times a day for 3 days; then 20mg four times a day as maintenance dose.

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

8. Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a molecule found on the surface of lymphocytes and monocytes. However, there was high incidence of infusion reactions and hematological toxicity.

9. Rituximab

Rituximab is a chimeric monoclonal IgG antibody derived from mouse/human that acts against the CD20antigen in B lymphocyte The CD20 marker is essential in B lymphocyte activation and differentiation. Rituximab has been useful in treating lymphoma, leukemia, multiple myeloma and chronic anterior uveitis refractive to steroids and other steroid agents[59], inducing patient with relapsing necrotizing scleritis associated with granulomatosis[60], and inducing remission of retinal vasculitis in patient with Behcet's disease.[61]

Drug is administered as an intravenous infusion, 375 mg/m2, every week for 4 weeks.

The common side effects include flu-like symptoms headache, nausea, fatigue and rash.

11. **Abatacept**

Abatacept is a soluble fusion protein composed of ligand binding domain of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and a fragment of human immunoglobulin.

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.

12. **Interferons**

Interferons (IFNs) have antiviral, anti-neoplastic, immunomodulatory and anti-angiogenic effects. It is used in treatment of refractory and sight threatening uveitis including both Behcet's and non- Bechet's cases according to a randomized control trial.[62]

Type 1 IFNs are commonly used in treatment of ocular inflammation and include IFN-β and IFN-α. These two subtypes increase the expression of the major histocompatibility class (MHC) 1surface molecules and activate natural killer cells (NK cells) and macrophages[60]. IFN-β and IFN-α therapy may lead to significant improvement in ocular inflammation and visual acuity.[64,65]–Patients with multiple sclerosis-associated experienced improvements in ocular inflammation, macular edema and visual acuity[66].

Common side effects include fatigue, flu-like syndromes, mood changes such as depression and medication-induced SLE, elevation of LFT, alopecia, neutropenia, lymphocytopenia and thrombocytopenia.

IFNa2a is given at dose of 3–6 million IU daily to three times a week[66]. Liver function tests, CBC and thyroid function tests should done prior to therapy initiation and then at 4- to 6-week intervals.

Oral S Antigen:

One small, randomized controlled trial on oral feeding with retinal S antigen demonstrated equivocal benefit in patients with uveitis[66] such as Pars planitis, Behcet's disease, Multiple sclerosis, Rheumatoid arthritis.

It is given 30 mg of S antigen 3 times a week. No specific significant toxic effects attributable to S antigen therapy has been reported.

Emerging Therapies

Recent developments in uveitis therapies have shifted focus to targeting inflammatory cytokines, T-cell activation, T-cell migration, downstream pathways by using small molecule inhibitors. Developments of antibodies generated against inflammatory cytokines involved in uveitis and other autoimmune diseases such as IL-17, IL-23, IL-22 and IL-6 have been under investigation and offer novel strategies.

Small molecule inhibitors of Janus kinases and protein kinases may offer strategies to modulate the intracellular downstream signaling.

Tofacitinib is FDA approved for rheumatoid arthritis and sotrastaurin currently studied in phase 2 trials in patients with macular edema associated with uveitis offer examples of this approach, respectively.

Small interfering RNA (siRNA) and microRNA technology can also be utilized to inhibit the expression of inflammatory cytokines[68]. Improved local drug delivery methods are also being advanced. Lee et al.[69] demonstrated the effectiveness of topical tacrolimus ointment in controlling refractory inflammatory ocular surface disease, such as scleritis and Mooren ulcer, and reducing inflammation recurrence and reliance on steroid use.

For the intravitreal route, trials of micro-particle injectable are being conducted. These can be in the form of drug-eluting micro particles with sizes of 1–10 lm, suspended in a liquid carrier or microspheres with drug–polymer associations dispersed within a polymeric matrix[67]. For example, Tethadur TM (pSivida, MA, USA) is a porous silicone micro-particle designed to have sustained release of proteins, peptides, chemical molecules and therapeutic antibodies. Intravitreal injections of a viscous gel or liquid can be formulated to release monoclonal antibodies and small peptides, proteins and molecules as demonstrated by the Verisome system (Icon Bioscience, Inc.CA, USA).[65,67]

Conclusions

Oral Corticosteroids represents one of the main stays in the treatment of severe ocular inflammation.However, chronic oral corticosteroid therapy is associated with several potential side effects, which may have adverse effect on the patient's long-term health. Therefore, many patients on chronic oral corticosteroids will require addition of an immunosuppressive drug, either because of the occurrence of these side effects or because of the need for a dose of oral corticosteroids, highly likely to result in long-term side effects. In selected diseases, such as Behcet's disease with posterior segment ocular involvement, the outcome of oral corticosteroid therapy alone is poor, that immunosuppressive drugs probably should be used from the outset. Because of the potential side effects and because of the different side effects of the different drugs, treatment must be individualized and regular monitoring performed. With careful use of these medications, many patients will benefit from them, either with better control of the ocular inflammation, or with a decrease in corticosteroid side effects.

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