

Guest Editorial

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Immunosuppressive Agents In Uveitis – My Experience

My experience with Immunosuppressive agents in uveitis started in 1989 after my return from USA completing fellowship in Doheny Eye Institute University of Southern California, Los Angeles. There I saw many patients being put on the azathioprine tablet. I had used immunosuppressive agent for the first time in a 12-year-old boy who had bow and arrow injury in one eye. That time there was Mahabharata Serial in TV and lot of children used to play with bow and arrow. The child lost vision due to injury in the left eye. Other eye lost vision after one month. The patient's grandfather became very worried and brought the child from Bihar to our institute. There was disc edema as well as vitreous haze and neuro sensory retinal detachment. I put the patient on tablet azathioprine (50mg) half tablet three times daily with low dose oral prednisolone. His disc edema revolved and the retina settled and the patient got back 6/6; N6 vision. I lost track of this patient. I was pleasantly surprised after 28 years; the patient saw my name in facebook and wrote to me that he is doing post doctoral fellowship at Switzerland. This was my first patient who received immunosuppressive therapy. I have also had bad experience with immunosuppressive agents. I had a 23 year

old patient of sarcoid uveitis whom I put on tablet mycophenolate mofetil. One month after the patient came with an extensive herpes zoster involvement involving the trunk and chest. I had to put the patient on tablet valacyclovir as well as steroid. He did show improvement but there was an extensive scarring due to herpes zoster skin lesion.

Subsequently, we also had another patient of Vogt–Koyanagi–Harada disease (VKH) disease who was put on tablet azathioprine and developed extensive herpes zoster lesion on the face. Another patient developed severe neutropenia following azathioprine and patient had to be admitted in an intensive care unit.

In immunosuppressive agents usage in uveitis and scleritis, one should know when to use it, what to use and how to use it. Immunosuppressive agents in anterior uveitis are usually not required except in recalcitrant cases. Also, it is used in anterior uveitis with juvenile idiopathic arthritis in which particularly methotrexate is quite useful. In recurrent anterior uveitis, Vogt–Koyanagi–Harada disease (VKH) disease and sympathetic ophthalmia one should put the patient on immunosuppressive agents with topical steroid and mydriatic cycloplegic agent. I follow an algorithm of usage for immunosuppressive agents in anterior uveitis. My first step is topical steroid and mydriatic cycloplegic agent, if not responding I add systemic steroid, if not responding I add immunosuppressive agents.

Recently there are some reports that the immunosuppressive agent methotrexate can be an option for preventing recurrence of anterior uveitis. I have used methotrexate in many patients with recurrent anterior uveitis. It does reduce the rate of recurrence. However, it doesn't completely relieve the patient from recurrence. In case of intermediate uveitis, immunosuppressive agents are the third step in a step ladder pattern. In first step, I use posterior subtenon injection of triamcinolone acetonide. Second step I use oral Prednisolone 1 mg per kg of body weight. If not responding, I add immunosuppressive agents with oral prednisolone. My choice of immunosuppressive agent in intermediate uveitis is mycophenolate mofetil. If not responding, I then switch over to azathioprine. If not responding, I switch over to cyclosporine tablet. Still if there is no response to the treatment, to control the inflammation and vitreous haze, I ask the patient to undergo therapeutic vitrectomy.

The top most indication of Immunosuppressive agents in uveitis is Behcet's disease, where oral steroid has got limited role. Other indications are sympathetic ophthalmia, Vogt Koyanagi Harada disease and juvenile idiopathic arthritis associated uveitis, serpiginous choroiditis after ruling out active tuberculosis and in chronic intermediate uveitis. There are three groups of immunosuppressive agents. First group is antimetabolites, second is alkylating agents and third is calcineurin inhibitor like cyclosporine and tacrolimus.

Antimetabolites are safer than alkylating agents. Alkylating agents cyclophosphamide and chlorambucil can cause marked

decrease in the WBC count and therefore may be risky unless blood count is monitored periodically. Antimetabolites have got their own side effects. Methotrexate has got hepatotoxicity and bone marrow suppression. Azathioprine also causes hepatotoxicity in addition to bone marrow suppression. Mycophenolate mofetil too can cause mild bone marrow toxicity. I use azathioprine at the dose of 1.5 to 2 mg per kg of body weight. One needs to remember that the onset of action is about 3 to 4 weeks. So you do not expect immediate improvement of vision following azathioprine. However after 3 to 4 weeks there is good control of inflammation with improvement of vision. One needs to get blood count and liver function test done every four weekly with tablet azathioprine. However to be on the safer side I ask the patient to get total WBC and platelet count done every two weeks. Tablet azathioprine can be continued for a longer time. If cyclophosphamide, an alkylating agent, is taken for more than 18 months, there is slight risk of malignancy. I have found good results with azathioprine and steroid combination in non infectious serpiginous choroiditis. In case of sympathetic ophthalmia, Azathioprine works very well to preserve the vision. Methotrexate is economical and is very suitable for patients in not on our country.

I have extensively used it for juvenile idiopathic arthritis-associated-uveitis, sarcoid panuveitis as well as scleritis. It has very convenient dosing regimen of orally once a week supplement with tablet Folvite (folic acid). One can give subcutaneous injection also. One needs to monitor total white blood cell and platelet count as well as liver function test once in a month. There was not is a trial comparing methotrexate and mycophenolate mofetil for non-infectious uveitis. They found 22% difference in the treatment success, favouring methotrexate. In that study mycophenolate mofetil was not in used in full dosage of one gram twice daily. Immunomodulators like cyclosporine and tacrolimus are very effective in T-cell mediated disease like VKH, sympathetic ophthalmia, Behcet's disease. I particularly use cyclosporine in Behcet's disease. Cyclosporine is given 5 mg per kilogram of body weight in two divided dosage. This can be reduced to 25 mg per month. The tablet is available in 100 mg as well as in 25 mg. One needs to monitor blood pressure and renal function test once a month. Another complication which it can cause is gingival hyperplasia. While brushing the teeth, patient complains of bleeding from the gums. Tablet mycophenolate mofetil is a relatively new immunosuppressive agent. It is extensively used by nephrologists quite frequently for kidney transplant patients. The action is similar to azathioprine but has lesser side effect; Weight loss and gastrointestinal upset are the major side effects. I give tablet mycophenolate mofetil 500 mg two tablet two times daily.

We have published a series of eight cases in 2000 add and found mycophenolate mofetil was safe and effective. I have more than 500 cases now treated with this drug to control uveitis and scleritis. What immunosuppressive agents to choose is quite important. I use tablet methotrexate for juvenile idiopathic arthritis, tablet cyclosporine for Behcet's disease, tablet azathioprine for serpiginous choroiditis and tablet mycophenolate mofetil for intermediate uveitis. One should be familiar with the immunosuppressive agents one is using. One should know the therapeutic action and adverse effects. Each immunosuppressive agent has got some specific side effects. For example, cyclosporine causes renal toxicity, Cyclophosphamide causes gonadal damage as well as haemorrhagic cystitis. Tablet mycophenolate mofetil can cause bone marrow suppression and gastrointestinal intolerance. Tablet azathioprine can cause bone marrow suppression and hepatotoxicity. Methotrexate can cause bone marrow suppression and hepatotoxicity. One can get hair loss with azathioprine and cyclophosphamide. I have seen patients with tablet azathioprine and cyclophosphamide getting extensive alopecia following the usage of those drugs. Earlier I was using tablet azathioprine frequently. Now I have switched to tablet mycophenolate mofetil in majority of my cases. The cost of treatment is also very important. While tablet prednisolone, tablet methotrexate, tablet cyclophosphamide, tablet azathioprine is quite reasonable, tablet cyclosporine and tablet mycophenolate mofetil is quite costly. The combination therapy is often used in case of recalcitrant non-infectious uveitis. I have used cyclosporine in combination with tablet. azathioprine and prednisolone. This can be effective in recalcitrant serpiginous choroiditis, Vogt-Koyanagi-Harada disease and sympathetic ophthalmia.

If the patient has been put on immunosuppressive agents it is very important to have periodic follow up with investigations as per the drug used. Physician review is important. One needs to promptly discontinue the treatment in case of serious side effect. The most important thing is the patient should not have an active infection like an active pulmonary tuberculosis or active focal sepsis.

In case of scleritis, I often use immunosuppressive agent if not responding to oral steroid. In particular, I use cyclophosphamide in case of necrotising scleritis. The dose is 50 mg tablet two tablets daily in the morning after breakfast. I ask the patient to take two liters of water to prevent bladder toxicity. My preferred drug of choice in scleritis is tablet mycophenolate mofetil 500 mg tablet two tablet two times daily. If not responding, I usually switch over to cyclophosphamide. However one can

use tablet azathioprine also. In case of recurrent scleritis, I have found methotrexate to be quite useful. We have analyzed our usages of immunosuppressive agents in our clinic. In an unpublished series of 259 consecutive patients, we have used 64 patients with immunosuppressive agents which come to about 25% approximately. Most common indication was intermediate uveitis. In Behcet's disease we have used immunosuppressive agents in 100 % cases.

A few words about biologic agents which have come in the armamentarium of uveitis. There can be used particularly in Behcet's disease, uveitis associated with ankylosing spondylitis, juvenile idiopathic arthritis associated uveitis. The drug is quite costly and one needs to rule out tuberculosis and hepatitis before starting the drug. Commonly used biologic agents are infliximab and adalimumab.

In conclusion, I feel immunosuppressive agents are quite important in the armamentarium in treating non-infectious uveitis and scleritis. But one needs to be cautious in usage of these agents particularly to see that total WBC count doesn't go below 1,500cells/mm³ and/or platelet count does not goes below 1,00,000/mm³. It is of paramount importance to rule out infectious etiology.

Suggested Readings

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