

## REVIEW ARTICLE

### Management challenges and future trends in uveitis

#### AUTHORS

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#### INTRODUCTION

For many years, uveitis was considered a single disease entity therefore the approach to treatment varied very little. Due to development and sophistication of immunologic and microscopic testing it is clear that uveitis entails a multitude of disease processes. Although some diseases are local ocular immune phenomena, many of them are systemic conditions with ocular manifestations. The spectrum of disease pathogenesis ranges from autoimmunity, neoplasms, to infections and therefore the practitioner of uveitis requires an understanding of internal medicine, infectious diseases, rheumatology and immunology. Uveitis though not as common as cataract and glaucoma often poses diagnostic and therapeutic challenges. The incidence of uveitis in western countries is 14 per 100,000 population and the prevalence of uveitis is 38 per 100,000 population.

In Africa there are no published reports on the epidemiological status of uveitis and due to the similar socio economic and health status between India sub-continent and the African region, we can refer to some of their epidemiological studies of uveitis. In the only urban population based study in South India, it was shown that of 2553 subjects, 21(0.73%) had active or inactive uveitis unrelated to previous surgery or trauma. Active uveitis was present in 8 subjects (0.37%) of whom 0.06% had anterior uveitis, 0.25% had intermediate uveitis and 0.06% had posterior uveitis. Prevalence of inactive uveitis 0.36% included macular chorioretinitis scar (0.26%) anterior uveitis (0.07%) and previous vasculitis (0.03%).<sup>1,2</sup>

In a tertiary referral eye care centre, uveitis accounted for 1.5% of the new cases seen in the Uveitis clinic. Out of 1273 uveitis cases in a three year period in Sankara Nethralaya anterior uveitis was most commonly observed (39.28%), followed by posterior uveitis (28.75%), intermediate

uveitis (17.44%) and panuveitis (14.53%). The most commonly affected age group was patients in their fourth decade ( 23.57%), whereas uveitis was less common in children below 10 years (3.61%) of age and in adults over 60 years of age (6.44%). There was a male preponderance of 6:4. Although etiology remained undetermined in 59.31% of cases, the commonest cause of posterior uveitis was toxoplasmosis (27.87%) and for panuveitis it was Vogt Koyanagi Harada syndrome (21.08%). In other studies<sup>3</sup>, there is a higher incidence (5 cases) of microbiologically proven tubercular uveitis and uveitis due to live intraocular nematodes (4 cases). Malaria has also been shown to cause uveitis in this study. Behcet's disease is far less commonly seen in the sub continent with only 4 cases having been seen at Sankara Nethralaya over a three year period.

Uveitis occurs at an age when patients are in their active working period of life. Approximately 80% of uveitis patients have the disease in the 20-60 years age group and in 50% the age of onset is the third or fourth decade of life. Uveitis patients do not suffer from ocular disease alone, 25% to 50% of these patients have underlying systemic diseases<sup>1</sup>

Uveitis comprises of 10% to 15% of all cases of total blindness in the United States<sup>1</sup> To the contrary percentage of blindness due to uveitis in the sub continent is still not known. Uveitis is known to cause several complications like complicated cataract, secondary glaucoma and choroidal neovascularization which can lead to visual impairment. Such complications sometimes require expertise from other subspecialties.

Not only the disease, but the treatment of uveitis is not without complications. While topical steroids used for control of anterior uveitis can produce secondary glaucoma and cataract, systemic steroids can produce

systemic side effects like cushingoid features, systemic hypertension, and diabetes mellitus.<sup>4</sup>

Immunosuppressive agents used in uveitis can sometimes produce life threatening complications like hypovolaemia, bone marrow suppression, nephrotoxicity and hepatotoxicity<sup>5</sup>

Another challenge to the ophthalmologist is finding the cause of uveitis. Not only can it occur due to several causes, the cause can remain oblivious in at least 30% of cases in spite of extensive laboratory investigations and systemic evaluation in the best of ophthalmic centres.<sup>1</sup>

Uveitis has a variable visual prognosis. While visual impairment can occur in 1% of patients with anterior uveitis, posterior uveitis can lead to severe visual impairment if not treated promptly.<sup>1</sup> In several uveitis entities like Behcet's disease, serpiginous choroiditis, acute retinal necrosis, progressive outer retinal necrosis and cytomegalovirus retinitis, patients do not have a good visual prognosis.

In this article we outline the main challenges in uveitis and how to overcome it.

## DIAGNOSTIC CHALLENGES IN UVEITIS

Uveitis can present with some of the most challenging diagnostic dilemmas in all of ophthalmology. One of the major diagnostic challenges in uveitis is to determine whether the condition is a uveitic entity or not. Conditions like retinoblastoma, leukaemia and ciliary body tumours can present as uveitis. We came across and analyzed 32 cases of non uveitic entities (1.2%) that had been misdiagnosed and referred as posterior uveitis out of 2846 outpatient of posterior uveitis registered from 1990 to June 2002. The correct diagnosis was finally achieved by careful history taking, slit lamp examination, meticulous fundus evaluation, imaging and ancillary studies. The final diagnosis included multiple leak central serous retinopathy (CSR) (25%), choroidal neovascular membrane (18.75%), typical central serous retinopathy (12.50%), dry form of age related macular degeneration (9.3%), retinitis pigmentosa (9.3%), myelinated nerve fibers (6.2%) and malignant melanoma of the choroids (3.1%).<sup>6</sup>

The majority of the referred cases of

misdiagnosed posterior uveitis had multiple leaks CSR. This condition can produce sub retinal fibrin deposits, which can mimic active patches of choroiditis. Careful slit lamp examination can invariably show absence of vitreous cells. Fundus fluorescein angiography is often diagnostic showing multiple pinpoint leaks in the mid arteriovenous phase and leakage in the late venous phase. The mainstay in treatment of non infectious posterior uveitis is steroids which can worsen this condition. Multiple leaks CSR with secondary retinal detachment require either observation or argon laser photocoagulation of the leakages.<sup>6</sup>

The wet types of ARMD can develop a CNVM. This condition can produce yellow or grey lesions with surrounding exudates and mimic posterior uveitis. Careful evaluation, however, can reveal the presence of haemorrhage. Such haemorrhage is quite uncommon in choroiditis. Moreover, vitreous cells are invariably absent in such conditions. Although these patients are usually over 50 years of age, only one of the six patients in our study was older than 50 years. Idiopathic CNVM can occur in young patients and diagnosis of such cases can be really challenging. Fundus fluorescein angiography or indocyanine angiography can reveal characteristic feature of CNVM. However, such a condition is relatively uncommon and usually such a neovascular membrane occurs several years after the disease. Endogenous endophthalmitis and large cell lymphoma can mimic panuveitis.

The next challenge is identification of the cause of uveitis which begins with the signs and symptoms followed by tailored investigations. One strategy used by nearly all clinicians is the formulation of a list of potential diagnoses from a brief interaction with the patient, followed by a focused history and examination. Then appropriate investigations shorten the list of diagnostic possibilities.

Although a thorough clinical and systemic examination cannot be overemphasized in uveitis, investigations, which includes laboratory test, ancillary investigations like fundus fluorescein angiography (FFA), ultrasound, imaging studies like optical coherence tomography are often necessary to identify the cause of uveitis.

Steps before ordering investigations include:

- Uveitis oriented history
- Complete ophthalmic examination
- Identification of anatomic location

and extent of uveitis

- An overall systemic evaluation
- Comparing the clinical characteristics with known uveitic entities
- Shortlist etiological possibilities
- Order first relevant investigations
- Order extensive investigations if refractory to treatment

One should not wait for the reports of laboratory tests to initiate treatment. Initial treatment can be started to prevent structural changes, like synechiae formation and macular involvement. Based on laboratory test results, appropriate treatment modifications can be made.

There are certain uveitic entities which may not require laboratory tests like Fuchs's heterochromic iridocyclitis, uveitis due to trauma, first attack on non granulomatous acute anterior uveitis, an unequivocal case of Vogt Koyanagi Harada Syndrome (VKH) and sympathetic ophthalmia.

No standard laboratory evaluations exist for the patient with uveitis, except in screening for syphilis and possibly sarcoidosis since both can present in a myriad of ways. There are certain laboratory tests which can be done in general to all uveitis patients. These are erythrocyte sedimentation rate (ESR) total and differential white blood cell count. In sclerouveitis cases rheumatoid arthritis should be excluded by doing Rheumatoid Factor test. In cases of suspected Wegener's granulomatosis serum anti neutrophilic cytoplasmic antibody (ANCA) levels should be determined.

#### 1. ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA) TEST

ELISA for toxoplasma or toxocara should be done in cases suspicious of toxoplasmic retinochoroiditis or toxocara uveitis. ELISA for HIV 1 & 2 should be done in cases of uveitis due to herpes zoster ophthalmicus, endogenous endophthalmitis, necrotizing retinitis and multiple cotton wool spots (HIV retinopathy). ELISA for tuberculosis has got little diagnostic value where there is high prevalence of exposure to tuberculosis. In normal healthy patients positive antibody titre to tuberculosis is often present.

#### 2. HUMAN LEUCOCYTES ANTIGEN (HLA) TYPING

HLA typing is a relatively costly test which should be done in selective cases like, HLA A29 in birdshot retinochoroidopathy where sensitivity is 90%, HLA B51 in Behcet's disease

and HLA B27 in recurrent non granulomatous anterior uveitis. <sup>7</sup>

#### 3. SERUM ANGIOTENSIN CONVERTING ENZYME (SACE) LEVELS

The test should be done in all cases of granulomatous uveitis, intermediate uveitis, choroidal granuloma, optic nerve head granuloma and retinal vasculitis. Systemic steroids administration may yield a false negative result. Serum lysozyme levels should be done concurrently as this may increase the sensitivity of diagnosing sarcoidosis. Relevant systemichistory should be taken to find out systemic involvement. Commonly there is hilar lymph node involvement and pulmonary involvement. In such cases Bronchio alveolar lavage can be done to determine a histological diagnosis. Conjunctival or lachrymal gland biopsies can also be very helpful in reaching a histopathological diagnosis of sarcoidosis.

#### 4. MANTOUX TEST (PURIFIED PROTEIN DERIVATIVE TEST)

A positive Mantoux test should be interpreted with caution as this test is positive in 30 to 65% of healthy subjects whereas negative or weakly positive in 33% of tuberculosis patients.

#### 5. QuantiFERON TB GOLD TEST

Recently a newer second generation test for the diagnosis of tuberculosis has been introduced known as the Quantiferon TB Gold test and approved by the FDA. It diagnoses both latent tuberculosis infection and tuberculosis diseases. This is an invitro test that measures a component of cell mediated immune reactivity to Mtb. Based on the quantification of interferon gamma (INF  $\gamma$ ) released from sensitized lymphocytes in whole blood incubated with purified protein derivatives from Mtb and control antigens. The antigens used include mixtures of synthetic peptides representing two M. tuberculosis proteins, the Early Secreted Antigen Target (ESAT -6) and Culture Filtrate Protein (CFP10). The advantages of the test are that it requires a single patient visit. It assesses response to multiple antigens simultaneously, does not boost anamnestic immune responses and is less subjective than Mantoux Test. The test is more likely to be positive than Mantoux Test in patients with active TB. This assay will not be positive in individuals vaccinated with BCG or infected with atypical Mycobacteria

#### 6. PCR FOR TUBERCULOSIS

IS6110 primer based PCR has been widely used for the detection of M tuberculosis complex of bacteria. However, the nested PCR technique

employing the MPB64 gene is 10,000 folds more sensitive and 100 % specific for the detection of Mtb. When the diagnosis is doubtful or in situations where identification of the etiological agent is necessary, nested PCR can be used.<sup>8,9,10</sup> Use of real-time PCR technology can help differentiate commensals and contaminants from infecting microbes. Sensitivity may also be improved by dot-blot hybridization of the PCR product by 32P-labeled specific probes.<sup>11</sup>

## 7. RADIOLOGICAL INVESTIGATIONS

This includes Chest X-Ray (CXR), CT (Computerised Tomography) scan, magnetic resonance imaging (MRI) and Gallium scan. CXR is done for diagnosis of tuberculosis and sarcoidosis, which can be associated with uveitis. Any patient who is put on systemic steroid or immunosuppressive agents should get a CXR done to exclude pulmonary tuberculosis which can get aggravated if put on above treatments. X ray of sacroiliac joint and spine is required in uveitis with ankylosing spondylitis. Spiral CT scans are more sensitive as it provides multidimensional view.

## 8. ANCILLARY TESTS IN UVEITIS

Ancillary tests are very useful for the diagnosis of uveitis. These comprise of fundus fluorescein angiography, indocyanine green angiography, ultra sonography (B scan), ultrasound biomicroscopy, optical coherence tomography, multifocal electro retinography.

### a. FUNDUS FLUORESCEIN ANGIOGRAPHY (FFA)

FFA is required for diagnosis of posterior uveitis, to determine the extent of involvement, in the retinal or choroidal lesions, to monitor the disease progression in choroiditis to identify the complication like choroidal neovascular membrane and cystoid macular oedema.

### b. INDOCYANINE GREEN ANGIOGRAPHY (ICG)

ICG angiography can detect new lesions and more extensive lesions than seen in clinical and FFA examination.<sup>12</sup> ICG increases the sensitivity of detecting occult CNVM secondary to uveitis particularly if obscured by haemorrhage.

### c. ULTRASONOGRAPHY (U/S)

B-Scan ultrasonography can determine choroidal thickness in sympathetic ophthalmia and VKH syndrome. In acute posterior scleritis, inverted 'T' sign will be positive whereas scleral thickening will indicate either chronicity or recurrent attacks of posterior scleritis. In cases of media haze obscuring the

view of the fundus B scan can detect vitreous opacities, membranes, retinal detachment, choroidal detachment and gross optic nerve head cupping.

Ultrasound bio-microscopy which is done with 50 MHz probe can be used to evaluate the pars plana and ciliary body in small pupils and complicated cataracts where the fundus cannot be seen with indirect ophthalmoscopy. It can detect exudates and membranes over the par plana indicative of pars planitis. In hypotony it can detect ciliary body atrophy or detachment. It is also useful in IOL induced uveitis to detect any malposition of the IOL haptic. It can also detect foreign body and caterpillar hair causing uveitis.<sup>13,14</sup>

### d. OPTICAL COHERENCE TOMOGRAPHY (OCT)

This is a relatively new tool in uveitis armamentarium. OCT can detect macular oedema, macular hole and panretinal membrane in uveitis in clear media. It is also very useful to monitor the changes in macula following therapy.

### e. MULTIFOCAL ELECTRORETINOGRAM

Multifocal electroretinography (mfERG) is useful in cases of macula threatening uveitis.<sup>15</sup>

### f. HISTOPATHOLOGY

Histopathology is not required routinely in uveitis and is indicated in selected cases only.<sup>16</sup> It can be done by anterior chamber tap, vitreous biopsy, fine needle aspiration biopsy (FNAB) and chorioretinal biopsy.<sup>17,18</sup> Such invasive histopathological studies are indicated in conditions like lens induced uveitis, uveitis of infectious aetiology, intraocular parasitic infestation, endophthalmitis and masquerade syndrome.

### g. PCR

Polymerase chain reaction (PCR) is a new tool in the armamentarium of the diagnosis of uveitis of infectious aetiology. PCR is a highly sensitive and specific technique which can be used to detect viral uveitis, tubercular uveitis, toxoplasma uveitis and delayed onset post surgical endophthalmitis/uveitis caused by Propionibacterium acne.<sup>19, 20</sup>

## THERAPEUTIC CHALLENGES IN UVEITIS

Ophthalmologists should make all attempts to preserve the structure and the function of the eye from the attacks of uveitis by:

- a) Prompt and adequate control of intraocular inflammation
- b) Prevent visual loss

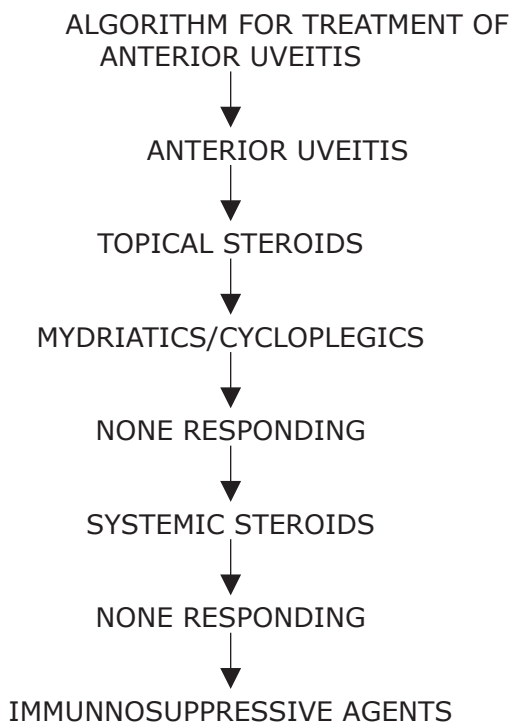
c) Minimize long term complication of diseases and its treatment.

The key issues in management are to decide:

- 5
- Whether uveitis, is active or inactive
- Infectious or non-infectious
- Vision threatening or not vision threatening
- Is there any complication due to uveitis
- Is there any systemic association with it

#### MANAGEMENT OF ANTERIOR UVEITIS

Management of anterior uveitis is often simple and straight forward. Frequent use of topical steroid with short acting mydriatic / cycloplegic agents is the mainstay of treatment. Prednisolone acetate which possesses biphasic solubility allows penetration of both the lipid and aqueous layers of tear film efficiently, hence the drug of choice. Prednisolone acetate can be administered as frequently as every 15 minutes. Topical steroids can then be gradually tapered according to the response. There are some soft steroids like Loteprednol etabonate and Remiexolone which causes less chance of intraocular pressure rise than Prednisolone acetate.<sup>21</sup> Non Steroidal Anti Inflammatory Drugs (NSAIDs) are not very useful in acute anterior uveitis due to their weak anti inflammatory effect. However, they can use as an adjunct to topical steroids in chronic low grade anterior uveitis.



Immunosuppressive agents are usually not required in anterior uveitis. They can be given only in recalcitrant cases of anterior uveitis,

anterior uveitis associated with juvenile rheumatoid arthritis, VKH and sympathetic ophthalmia.

#### MANAGEMENT OF INTERMEDIATE UVEITIS

Management of intermediate uveitis can be done in a modified four step approach (Kaplan).<sup>17</sup> First step – posterior sub-tenon injection of depot steroid (Triamcinolone acetonide, 40mg / ml). Second step – oral Prednisolone (1mg /kg body weight/day). Third step- immunosuppressive agents. Fourth step – indirect laser / cryotherapy / vitrectomy. Posterior subtenon injection is given by using Nozik's technique in upper temporal quadrant asking the patient to look down and it can be repeated once in 3 weeks.

#### MANAGEMENT OF POSTERIOR AND PANUVEITIS

Systemic steroid remains the mainstay of treatment in majority of cases of posterior and panuveitis.<sup>17</sup> Prednisolone is the drug of choice; given at a dose of 1 mg / kg body weight per day every morning after breakfast. Peak effect is reached in 1 to 2 hour. It is usually tapered at a rate of 10 mg / week. Some patients may need low dose prednisolone for a long time (3-4 months) at the doses of 10 to 15 mg / day. Counselling the patient about the side effects of steroids is mandatory. Ophthalmologist need to tell the patient that his face and body may be swollen, he / she may develop acne, check his / her blood pressure and blood sugar checked weekly.<sup>4</sup>

A tapering schedule of oral prednisolone is given below .22

60mg/day x 1 week	}	Taper 10mg / week
50mg/day x 1 week		
40mg/day x 1 week		
35mg/day x 1 week	}	Taper 5mg / week
30mg/day x 1 week		
25mg/day x 1 week		
20mg/day x 1 week		
15mg/day x 1 week	}	Taper 2.5mg / week
12.5mg/day x 1 week		
10mg/day x 1 week		
20mg on alt day x 1 week		
15mg on alt day x 1 week		
10mg on alt day x 1 week		

Systemic steroids can produce multiple side effects on the body. The most dreadful side effect is aseptic necrosis of the head of femur. Calcium supplement can prevent this side effect. In spite of various side effects, systemic steroid is often the best choice in the treatment of non infectious posterior and panuveitis. This is due to greater general experience with this drug, quick action, low cost, and relative safety.<sup>4</sup>

#### 1. INTRAVENOUS METHYL PREDNISOLONE (IVMP)

IVMP is required when quick anti inflammatory action is needed. The dose is 500mg to 1 gram intravenous infusion with 0.9% normal saline or sodium lactate solution over 30 to 60 minutes daily for 3 consecutive days. It should be given in an intensive care unit set up to be able to manage any cardio -pulmonary complication. IVMP should be followed by high dose oral steroid or immunosuppressive agent.<sup>23</sup>

#### 2. IMMUNOSUPPRESSIVE AGENTS:

Prerequisites for the use of immunosuppressive agent are absence of infection, absence of hepatic and haematological contraindications, facilities for follow up, informed consent,

reversibility of the disease process. Although these agents may be associated with serious complications, they are extremely effective in treatment of ocular inflammatory disease in which patient is either unresponsive or intolerant to systemic corticosteroid. Serious complications include renal and hepatic toxicity, bone marrow suppression, and increased susceptibility to infection. In addition alkylating agents may cause sterility and increased risk of future malignancy. Immunosuppressive agent are mostly used in Behcet's disease, sympathetic ophthalmia, Vogt Koyanagi Harada(VKH) syndrome, Juvenile rheumatoid arthritis [JRA) associated uveitis, recalcitrant pars planitis or serpiginous choroiditis'

Immunosuppressive agents are of three groups:

**Antimetabolites:** Methotrexate, Azathioprine, Mycophenolate mofetil.  
**Alkylating Agents :** Cyclophosphamide, Chlorambucil.  
**Immunomodulators :** Cyclosporine, Tacrolimus

**Azathioprine:** The onset of action is 3- 4 weeks. Dose is 1.5 to 2 mg / kg body weight. Total leukocyte count (TLC) and platelet count, liver function test every 3 to 4 weeks. The drug needs to be continued for 6 months to one year.

**Methotrexate:** It is the most economic immunosuppressive agent. It is given orally once a week. The peak effect of methotrexate on controlling intraocular inflammation may take 6-8 weeks. It is supplemented with folic acid. Monthly, liver function test (LFT), total leukocyte count and platelet count need to be done.<sup>24</sup>

MTX is indicated in JRA associated uveitis, Sarcoid uveitis, scleritis and panuveitis.<sup>21</sup> Dose is 7.5mg / week in children and 15mg / week in adults, given as a single oral dose. It can be also given subcutaneously, intramuscularly, or intravenously.

**Cyclophosphamide:** Dose is 2 mg / kg body weight / per day (100 mg / day in a single morning dose). It is commonly indicated if the other immuno modulators fail to control uveitis or as a first line therapy for necrotizing scleritis and uveitis associated with Wegner's granulomatosis. Monthly TLC, platelet counts and urine for microscopic blood must be done. If TLC counts fall below 2500/ $\mu$ L, cyclophosphamide should be discontinued

until the counts recover. Patients are advised to drink at least 2 to 3 litres of water per day to prevent hemorrhagic cystitis.

**Cyclosporine:** It acts on effector T Cells by stimulating interleukin 2. It is a very effective steroid sparing agent commonly used in combination with oral prednisolone. Monthly blood pressure and renal function test (blood urea/ creatinine) must be done. Dose is 5 mg / kg/ day. Peak blood levels are reached in 6 hours.<sup>22</sup>

**Mycophenolate mofetil:** It is a newer immunosuppressive agent. Its action is similar to azathioprine with fewer side effects. The main side effect is gastro intestinal upset. Dose is 1 gram twice daily.<sup>25</sup>

The choice of immunosuppressive agents should depend on familiarity with the drug, therapeutic action and adverse effects. Side effects are common.<sup>19-22</sup>

#### SIDE EFFECTS OF COMMON IMMUNOSUPPRESSIVE AGENTS

	CYCLOSPORINE	CYCLOPHOSPHAMIDE	AZATHIOPRINE	METHOTREXATE
GI intolerance	+	+	++	-
Hair Loss	-	++	-	-
Bone marrow suppression	-	++	+	+
Renal damages cystitis	++	-	-	-
Hepatotoxicity		-	+	+
Cystitis	-	++	-	-
Gonadal damage	-	++	-	-

Our choice of immunosuppressive agent in uveitis is azathioprine. This is due to its limited range of side effects, mainly bone marrow toxicity, and its reasonable cost.

It is usually given 50 mg thrice a day for 1 to 2 months, followed by 50mg twice a day for 1 to 2 months and then 50 my once a day for the next 1 to 2 months.

One may use combination therapy of 2 to 3 immunosuppressive agents in vision threatening, recalcitrant uveitis. Triple agent immunosuppressive therapy has been used in serpiginous choroiditis.<sup>27</sup>

Immunosuppressive therapy should be monitored periodically with investigations tailored for the immunosuppressive agent used. A rheumatologist/physician should review the patient periodically. In case of serious side effects, the immunosuppressive agent should be discontinued.

### NEWER THERAPEUTIC MODALITIES

Intravitreal sustained release drug delivery devices have a rate controlling membrane which deliver drug by diffusion mechanisms. Commonly used drug delivered by this route are.<sup>28</sup>

- 1) Fluocinolone acetonide
- 2) Dexamethasone.

### FLUCINOLONE ACETONIDE SUSTAINED DRUG DELIVERY DEVICE

This is a promising new therapy for the treatment of severe uveitis. Flucinolone acetonide devices release the drug at a rate of approximately 2 microgram per day. Pure drug is compressed in a 1.5 mm pellet which is then coated in polyvinyl alcohol and silicon laminated and affixed to a polyvinyl alcohol suture strut. The assembly is heat treated at 35 degrees for 5 hours to change the PVA crystalline structure and to control drug delivery rate further and then gamma ray sterilized. Release occurs through a diffusion port in the coating. It is surgically implanted through the pars plana in to the vitreous cavity of the patient.

Favourable effects on inflammation, preservation or the improvement of visual acuity, reversal of CME, reduction or elimination of topical, periocular or systemic anti inflammatory medications or a combination thereof are observed. Raised intraocular pressure and endophthalmitis are the major risks involved.<sup>29</sup>

### POSURDEX

It is a novel intravitreal drug delivery system (DDS). The dexamethasone posterior segment drug delivery system (DEX PS DDS) has been developed which gradually releases 350 or 700 microgram of dexamethasone after it has been inserted into the eye through a small pars plana incision or puncture. In preclinical studies of this delivery system, dexamethasone was detected in the vitreous up to 6 months after insertion.<sup>30, 31</sup>

The dexamethasone drug delivery system consists of dexamethasone in biodegradable polymer matrix extruded as filament. It has shown favourable effects on improvement of visual acuity and reduction of cystoid macular oedema in a phase 2 trial.<sup>30,31</sup> Phase 3 trial is still going on.

### INTRAVITREAL TRIAMCINOLONE ACETONIDE (IVTA)

Based on the experimental studies as well as clinical experience intravitreal injection of triamcinolone acetonide has increasingly been reported as a treatment of intraocular neovascular, oedematous or inflammatory disease. It can be used for chronic cystoid macular oedema (CME) due to uveitis. Complete resolution of CME has been reported in a significant proportion in majority of case series. Commonly used doses are 4mg / 0.1 ml and 2 mg / 0.5 ml.

One needs to monitor intraocular pressure following injection of triamcinolone Rise of IOP is logically less in lesser doses. Endophthalmitis is also a major risk involved after intravitreal triamcinolone injections.

### BIOLOGICS

We now have a much greater understanding of the inflammatory cascade, including cytokines produced by activated CD4+ T lymphocytes such as tumour necrosis factor  $\alpha$  (TNF  $\alpha$ ), interferon gamma (IFN- $\gamma$ ), interleukin 1 (IL-1), interleukin 2 (IL-2) and interleukin 10 (IL-10). Biologics are proteins produced by recombinant DNA or monoclonal antibody technology directed against specific cytokines or their receptors. Currently in use are infliximab, etanercept, daclizumab and adalimumab.<sup>33</sup>

### TNF $\alpha$ ANTAGONIST

#### INFLIXIMAB

This is a genetically engineered fusion protein consisting of the TNF receptors fused to the constant region of human immunoglobulin IgG 1. Infliximab is found to be effective as a short term immunosuppressive agent in non infectious uveitis. Few studies have shown favorable results but there is a high chance of reactivation of granulomatous infections in patients taking infliximab. Other serious side effects reported are pulmonary embolism, congestive heart failure, lupus like reaction and vitreous haemorrhage. There are chances of development of antinuclear antibodies in patients receiving multiple infusions.

Dosage – 5 mg / kg

First day – first dose, at 2 week – Second dose, at 6 week – third dose administered as an intra venous infusion.

**ETANERCEPT**

Although Etanercept has been proven to be effective for the rheumatologic manifestations of rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis, its efficacy in uveitis appears to be limited.

Mechanism of action: Human TNFRp75 IgG1 fusion protein binds TNF  $\alpha$ . and TNF  $\alpha$ .

Dose and route: 25mg twice weekly, subcutaneous (SC).

Common adverse effects: Risk of infection, local reaction.

**INTERLEUKIN RECEPTOR ANTAGONISTS****DACLIZUMAB**

A recombinant monoclonal antibody interleukin-2 receptor antagonist.

Mechanism of action: Daclizumab binds specifically to the alpha subunit of the human interleukin-2 (IL-2) receptor expressed on the surface of activated lymphocytes *in vivo*, thereby inhibiting IL-2 binding and IL-2-mediated lymphocyte activation, a critical cellular immune response pathway.

Dose and route: 1mg/kg every four weeks, IV.

Common adverse effects: Risk of infection, allergic reaction.

**INTERFERONS**

Interferons are natural cytokines produced by the cells of the immune system in response to viruses, parasites and tumour cells. Interferon has antiviral and immunomodulating effects. It may be divided into alfa, beta, and gamma interferons. Interferons used for treatment is generally made by genetic engineering and usually consists of one type of alfa interferon only. Mechanism of action: Suppression of T helper 1 or increase in T helper 2 cytokines production: net anti-inflammatory response. Dose and route: 3 million units three times weekly, SC/IV.

Common adverse effects: Flu-like illness, leukopenia.

**MANAGEMENT OF INFECTIOUS UVEITIS**

Management of infectious uveitis is equally challenging. This includes treatment of viral retinitis, toxoplasmic retinochoroiditis, tubercular choroiditis. Oral steroid may be used with anti infective agents to control the inflammation associated with infectious uveitis.

**TREATMENT OF VIRAL RETINITIS (ACUTE RETINAL NECROSIS, PROGRESSIVE OUTER RETINAL NECROSIS)**

Intravenous acyclovir is the main stay of therapy in such cases. Dose is 750 mg as loading dose then 500 mg 8 hourly for 2 weeks (7 to 14 days)> it is given by intravenous infusion as a sodium salt. It should not be given by rapid or bolus injection. 500 mg acyclovir is dissolved in 500ml NS (0.9% normal saline) and then slowly infused over one hour. Patient should be adequately hydrated during and after infusion.

Intravenous therapy should be followed by therapy with oral acyclovir 800mg 5 times a day for 6 weeks. A newer oral antiviral drug, valacyclovir (L-valyl ester of acyclovir), has better bioavailability than acyclovir and is found to be comparable to intravenous acyclovir therapy in various studies. It I used in the doses of 1 gram three times a day for 6 to weeks.<sup>35, 36</sup>

**TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS**

CMV retinitis is one of the leading causes of ocular morbidity in AIDS patients. Ganciclovir is the drug of choice to treat this infection. Intravenous ganciclovir 10 mg / kg is given 12 hourly for first 10 to 14 days followed by 10 mg / kg / once daily as a maintenance therapy. It should be slowly infused over one hour with normal saline solution. The Patient should be well hydrated. Dose should be reduced in patients with renal failure.

Oral drug valganciclovir is also very effective in treatment of CMV retinitis and is as effective and to some extent even better than intravenous ganciclovir. It is given in the doses of 900 mg twice daily for first 3 weeks, followed by 900mg once a day as maintenance therapy. Intravitreal ganciclovir in the doses of 2 mg / 0.1 ml to 4 mg / 0.1 ml given weekly is also an effective therapy in cases of CMV retinitis.

**TREATMENT OF TOXOPLASMIC RETINOCHOROIDITIS**

This protozoan retinochoroiditis can be effectively treated by a variety of anti infective agents. Commonly used drugs are Pyremethamine with Sulphadiazine or a combination of Sulphamethoxazole(800mg) and Trimethoprim(40mg) which is known as Cotrimoxazole along with Clindamycin and/ or Azithromycin. We usually use Clindamycin 300mg 6 hourly for 6 weeks either as a mono therapy or in combination with Azithromycin 500mg as loading done followed by 250mg daily for 6 weeks. Clindamycin can also be

combined with Cotrimoxazole given as a twice daily dose for 6-8 weeks.<sup>37, 38</sup>

There is risk of development diarrhoea in patient takings Clindamycin which should be explained to the patient and one may need a physician's opinion for persistent diarrhoea. Spiramycin administered as 1 gram twice daily for 4 to 6 weeks is the drug of choice in cases of pregnancy.

## CONCLUSION

Although uveitis is a rare disease in comparison to cataract and glaucoma, it produces diagnostic and therapeutic challenges to all ophthalmologists including uveitis specialist. Careful history (uveitis oriented history), detailed ophthalmic examination, tailored laboratory investigations, judicious use of ancillary tests, prompt and adequate control of uveitis can preserve vision and prevent anatomic damage caused by uveitis.

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