MANAGEMENT OF UVEITIS

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Management of uveitis

1. What are biological immunosuppressive. Name few of them, as used in management of uveitis. J2009
2. a) Indications, routes of administration, dosage schedule and complication of steroids in uveitis.
   b) Role of alternative drugs used in uveitis. [(2+2+2) +2] J2015

Corticosteroids

- Corticosteroids are the mainstay of uveitis therapy.
- These drugs should be used only when the benefits of therapy outweigh the risks of the medications themselves
- Because of their potential adverse effects, however, they should be reserved for specific **indications**:
  1. **treatment of active inflammation in the eye**
  2. **prevention or treatment of complications such as CME**
  3. **reduction of inflammatory infiltration of the retina, choroid, or optic nerve**
- Corticosteroids are not indicated in patients with chronic flare or for the therapy of specific diseases such as Fuchs heterochromic uveitis or pars planitis not accompanied by macular edema.
- To reduce the complications of therapy, patients should be maintained on the minimum dosage needed to control the inflammation.
- 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.
- 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.

- **Routes-** Topical administration, periocular administration, intravitreal injections, systemic steroids.

1. Topical administration

- Topical corticosteroid drops are effective primarily for anterior uveitis, although they may have beneficial effects on vitritis or macular edema in some eyes.
- These drops are given at intervals ranging from once daily to hourly.
- The drugs can also be administered in ointment form for nighttime use or when preservatives in the eyedrops are not well tolerated.
- Difluprednate, 0.05%, a fluorinated corticosteroid, is highly potent; dosing at 4 times daily is considered the equivalent of 8 or more total drops per day of prednisolone acetate, 1%.
- Clinical studies suggest difluprednate has a similar adverse effect profile to prednisolone but is associated with potentially higher rises in IOP.
- Of the topical preparations, rimexolone, loteprednol, and fluorometholone have been shown to produce a smaller ocular hypertensive effect than that of other medications.
- However, these drugs are not as effective as prednisolone in controlling uveitis that is more intense than mild to moderate.
- Some generic forms of prednisolone may have less of an anti-inflammatory effect than that of the brand name products; this difference should be considered when the uveitis does not respond adequately to topical corticosteroid therapy.
- Differences in efficacy may be a result of differences in particle size among various suspensions and may necessitate more vigorous agitation of the drug before instillation.

2. Periocular administration

- **Indications**
  1. Periocular corticosteroids are generally given as depot injections when a more posterior effect is needed
  2. Or a patient is nonadherent or unresponsive to topical or systemic administration.
  3. These injections are often preferred for patients with intermediate or posterior uveitis or CME because they deliver a therapeutic dose of medication close to the site of inflammation.

Drugs	Approach
Triamcinolone acetonide (40 mg) Methylprednisolone acetate (40–80 mg)	1. Transseptal 2. Sub-Tenon (Nozik technique) approach- ➢ superotemporal quadrant (the preferred location), ➢ Inferotemporal quadrant

- Technique and complications of procedure - from Kanski
- **Contraindications**
  1. Periocular injections should not be used in cases of infectious uveitis (eg, toxoplasmosis) and

2. They should be avoided in patients with necrotizing scleritis because scleral thinning and perforation may result.

- **Complications**
  1. Periocular corticosteroids can cause systemic adverse effects similar to those of oral corticosteroids.
  2. 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).
  3. 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, although subconjunctival administration is generally not performed because of the risk of subconjunctival migration of the steroid vehicle.

3. Intravitreal injection administration

- **Indication-** Published literature on intravitreal triamcinolone administration suggests a definite treatment benefit, although of limited duration, for recalcitrant uveitic CME.
- **Drug-, dose, route-** Single trans–pars plana intravitreal injections of triamcinolone (4 mg; 0.1 mL) may produce sustained visual acuity improvements for 3–6 months in non-vitrectomized eyes.
- CME may recur after 3–6 months.
- **Complications**
  1. Repeated injections increase the risk of cataract formation in phakic eyes, and IOP elevation may occur transiently in more than one-half of patients.
  2. Complications such as "sterile endophthalmitis" may occur in 1%–6% of patients, but the incidence has dramatically declined since the introduction of a US Food and Drug Administration (FDA)–approved, preservative-free intravitreal triamcinolone.
  3. Infectious endophthalmitis and rhegmatogenous retinal detachment may occur, but these complications are rare when proper technique is used.
  4. This method of treatment is not curative of chronic uveitic conditions and should be used judiciously, as its effects are relatively short-lived.

4. **Intravitreal Implants**

a) **Fluocinolone implant**

- The sustained-release **fluocinolone implant** was approved by the FDA in 2005
- **Indication -** for the treatment of chronic noninfectious uveitis affecting the posterior segment
- **Route-** The implant is inserted through a small pars plana incision and sutured to the sclera.
- **Dose-** 0.59-mg implant is effective for a median of 30 months, with a mean time of 38 months to first recurrence. Reimplantation may be performed
- **Complications-**
  1. Phakic eyes developed cataract within 2 years after implantation.
  2. Elevated IOP necessitating topical therapy developed in nearly 75% of patients after 3 years, and 37% required filtering surgery.
  3. Postoperative complications such as endophthalmitis, wound leaks, hypotony, vitreous hemorrhage, and retinal detachments have been reported.

b) Dexamethasone implant

- A biodegradable intraocular implant containing 700 µg of dexamethasone is approved by the FDA and in Europe
- **Indication-**for the treatment of uveitis affecting the posterior segment of the eye and retinal vein occlusion.
- **Route-**This implant is injected through the pars plana into the vitreous cavity using the provided injector.
- **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.

5. Systemic administration

- **Route-** Oral or intravenous therapy may supplement or replace other routes of administration. To be given in consultation with an internist/ rheumatologist

- **Indications**
  1. Threatening chronic uveitis when topical corticosteroids are insufficient
  2. Or when systemic disease also requires therapy;

- **Dose**

1. If systemic drugs are used, the dosing and taper should be individualized to the patient.
2. Many oral corticosteroid formulations are available; prednisone is the most commonly used.
3. Most patients require 1–2 mg/kg/day of oral prednisone, usually no higher than 60–80 mg daily, which is gradually tapered every 1–2 weeks.
4. The lowest possible dose that will control the ocular inflammation and minimize adverse effects is desired.
5. Treatment with corticosteroids may last for 3 months or, in some cases, longer.
6. **If corticosteroid therapy at a level of 10 mg or more per day is required for longer than 3 months, immunomodulatory therapy (IMT) is indicated.**
7. In cases of an explosive onset of severe noninfectious posterior uveitis or panuveitis, 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.

- **Complications, side effects and their management**
- **IVMP**- adverse effects are numerous and can be life-threatening &include psychological disturbances, hypertension, and elevated glucose levels. This therapy should be performed only in a hospital setting by personnel experienced with this approach and its potential adverse effects.
- **Patients at high risk for corticosteroid-induced exacerbations** of their conditions are those with a propensity toward or manifest diabetes mellitus; patients with hypertension, peptic ulcer, or gastroesophageal reflux disease; those who are immunocompromised (from acquired or congenital causes); and patients with psychiatric conditions. Corticosteroids should be avoided, if at all possible, in these patients.
- **Patients taking systemic corticosteroids and NSAIDs concomitantly** have a higher risk of gastric ulcers, so this combination is best avoided; if necessary, these patients should receive a histamine-2 receptor blocker or proton-pump inhibitor.
- Patients receiving long-term corticosteroid maintenance therapy should supplement their diets with calcium and vitamin D to lessen the **risk of 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)
  - follicle-stimulating hormone and testosterone levels (if gonadal status is uncertain)
  - bone-mineral-density screening (for anyone receiving corticosteroid therapy for more than 3 months)
- The FDA has approved several drugs for prevention and treatment of corticosteroid-induced osteoporosis in men and women. These medications may be administered to at-risk patients receiving the equivalent of 7.5 mg or more of daily prednisone.

Immunomodulatory (immunosuppressive) therapy

- **Indications-** The use of IMT in uveitis is warranted for consideration in the following settings:
  1. vision-threatening intraocular inflammation
  2. disease process that is likely reversible
  3. inadequate response to corticosteroid treatment
  4. failure of therapy
  5. corticosteroids contraindicated because of systemic problems or intolerable adverse effects
  6. unacceptable corticosteroid adverse effects
  7. long-term corticosteroid dependence

- **Early use of IMT in**,

1. ocular cicatricial pemphigoid, 2. serpiginous choroiditis	3. Behçet disease, 4. sympathetic ophthalmia	5. VKH syndrome, 6. necrotizing scleritis associated with systemic vasculitis

- Although these disorders may initially respond well to corticosteroids, the initial treatment of these entities with IMT has been shown to improve long-term prognosis and lessen visual morbidity.
- **Relative indications**
- Conditions that do not respond adequately to initial corticosteroid treatment and cases in which patients incur serious corticosteroid-induced adverse effects.
- Examples include intermediate uveitis (pars planitis), retinal vasculitis, panuveitis, and chronic anterior uveitis.

Drugs

Antimetabolites	Inhibitors of T cell signaling	Alkylating agents	Biologic response modifiers
Azathioprine, Methotrexate, Mycophenolate mofetil, Leflunomide	Cyclosporine, Tacrolimus, Sirolimus	Cyclophosphamide Chlorambucil	Etanercept Infliximab Adalimumab Rituximab Anakinra Tocilizumab Intravenous immunoglobulin (IVIG) Interferon alfa-2a/2b (IFN-α2a/b)

Precautions before initiating IMT

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

1. an absence of infection
2. an absence of hepatic and hematologic contraindications
3. 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
4. informed consent

- There may be a delay in therapeutic response for weeks to months after initiation of IMT; therefore, most patients need to be maintained on corticosteroids until the immunomodulatory agent begins to take effect, at which time the corticosteroid dose may be gradually tapered.
- Because of the potentially serious complications associated with the use of IMT, patients must be monitored closely by a practitioner experienced with IMT.
- Blood monitoring, CBC, LFT, RFT, should be performed regularly.
- Serious complications include renal and hepatic toxicity, bone marrow suppression, and increased susceptibility to infection.
- Alkylating agents may cause sterility and were associated in earlier studies with an increased risk of future malignancies such as leukemia or lymphoma.
- Trimethoprim-sulfamethoxazole prophylaxis against Pneumocystis jirovecii (previously known as Pneumocystis carinii) infection should be considered in patients receiving alkylating agents.
- All of these medications are potentially teratogenic, and women should be advised to avoid becoming pregnant while taking them.

1. **Antimetabolites**

- Retrospective series report that compared with the other antimetabolites, azathioprine has a slightly higher incidence of adverse effects and Mycophenolate mofetil has a significantly shorter time to treatment success.
- Antimetabolites are often the first immunomodulatory therapies used when corticosteroid sparing is desired.

a) Azathioprine,

- **MOA-** a purine nucleoside analogue interferes with DNA replication and RNA transcription.
- **Dose, route**-It is administered at a dose of up to 2 mg/kg/day in adults. It is well absorbed orally
- **Indications**

1. In a randomized, placebo-controlled trial in patients with **Behçet disease**, it was shown to be effective in preventing ocular involvement among patients without eye disease and in decreasing the occurrence of contralateral eye involvement among patients with unilateral Behçet uveitis.
2. Azathioprine has also been found beneficial in patients with **intermediate uveitis, VKH syndrome, sympathetic ophthalmia, and necrotizing scleritis.**

- **Advantage-** Overall, nearly 50% of patients treated with azathioprine achieve inflammatory control and are able to taper prednisone dosage to 10 mg/day or less.

- **ADR, complications**

1. Many clinicians start administering azathioprine at 50 mg/day for 1 week to watch for development of any gastrointestinal adverse effects (nausea, upset stomach, and vomiting) before escalating the dose.
2. These symptoms are common and may occur in up to 25% of patients, necessitating discontinuation.
3. Bone marrow suppression is unusual at the doses of azathioprine used to treat uveitis.
4. However, patients taking allopurinol and azathioprine concomitantly are at higher risk for bone marrow suppression.
5. Reversible hepatic toxicity occurs in less than 2% of patients, and dose reduction may remedy mild hepatotoxicity.

- **The variability of clinical response to azathioprine** among patients is probably caused by genetic variability in the activity of 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 (0.3% of patients); azathioprine therapy not recommended
  - intermediate TPMT activity (11% of patients); azathioprine therapy at reduced dosage
  - normal/high TPMT activity (89% of patients); azathioprine therapy at higher doses than in patients with intermediate TPMT activity

b) Methotrexate

- **MOA-** 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**

1. Numerous studies have shown methotrexate to be effective in treating various types of uveitis; **JIA associated anterior uveitis, sarcoidosis, panuveitis, and scleritis.**
2. The drug has a long record of success in the treatment of children with JIA.
3. **For that reason, it has been a first-line choice for IMT in children**

- **Dose, route**

1. It is given as a weekly dose, usually starting at 10–15 mg/week and gradually increasing to a maintenance dose of 15–25 mg/week in adults.
2. The dosing is variable in children and depends on body surface area.
3. Methotrexate can be given orally, subcutaneously, intramuscularly, or intravenously and is usually well tolerated.
4. It has greater bioavailability when given parenterally.
5. Folate is given concurrently at a dose of 1 mg/day to reduce adverse effects.
6. Methotrexate may take up to 6 months to produce its full effect in controlling intraocular inflammation.

- **ADR**

1. Gastrointestinal distress and anorexia may occur in 10% of patients.
2. Reversible hepatotoxicity occurs in up to 15% of patients, and cirrhosis occurs in less than 0.1% of patients receiving methotrexate long-term.
3. Methotrexate is teratogenic, and complete blood counts and liver function tests should be conducted regularly.

- **Advantages**

1. Uncontrolled clinical trials have shown that it can enable corticosteroid sparing in two-thirds of patients with chronic ocular inflammatory disorders.
2. Recently, a prospective study of intravitreal injections of methotrexate (400 µg) for the treatment of refractory uveitis and uveitic CME demonstrated a reduction of inflammation and CME and well as a reduced need for systemic IMT.

c) Mycophenolate mofetil

- **MOA-**inhibits both inosine monophosphate dehydrogenase and DNA replication.
- **Dose**
- It has good oral bioavailability and is given at a dose of 1–1.5 g twice daily in adults.
- It tends to work rapidly; median time to successful control of ocular inflammation (in combination with less than 10 mg/day of prednisone) is approximately 4 months.

- **ADR**
- Less than 20% of patients receiving mycophenolate mofetil have adverse effects—reversible gastrointestinal distress and diarrhea are common—and these can usually be managed by dose reduction.

- Very few patients find the drug intolerable.
- **Advantage**
- Two large, retrospective studies found mycophenolate mofetil to be 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.

2. Alkylating agents

- **Indications**
- These drugs are generally used only if other immunomodulators fail to control uveitis;
- They are also used as first-line therapy for necrotizing scleritis associated with systemic vasculitides such as granulomatosis with polyangiitis (formerly, Wegener granulomatosis) or relapsing polychondritis.
- They have been found beneficial as well in patients with intermediate uveitis, VKH syndrome, sympathetic ophthalmia, and Behçet disease.
- **ADR**
- The most worrisome adverse effect of alkylating agents is an increased risk of malignancy.
- With the doses and durations used for the treatment of uveitis, the risk is probably low.
- Patients with polycythemia rubra vera treated with chlorambucil had a 13.5-fold greater risk of leukemia.
- Patients with granulomatosis with polyangiitis treated with cyclophosphamide had a 2.4-fold increased risk of cancer and a 33-fold increased risk of bladder cancer.
- Therefore, these drugs should be used with great caution and only by clinicians experienced in the management of their dosing and potential toxicity.
- Patients may wish to consider sperm or embryo banking before beginning cyclophosphamide or chlorambucil therapy because of the high rate of sterility if the cumulative dose exceeds certain limits.

a) Cyclophosphamide

- **MOA**

1. It is an alkylating agent whose active metabolites alkylate purines in DNA and RNA, resulting in impaired DNA replication and cell death.
2. Cyclophosphamide is cytotoxic to resting and actively dividing lymphocytes.

- **Indication**- Cyclophosphamide has been shown to be effective in treating **necrotizing scleritis, retinal vasculitis, mucous membrane pemphigoid,** and other uveitic conditions in uncontrolled case series.
- **Dose, route**

1. It is absorbed orally and metabolized in the liver into its active metabolites.
2. It is probably more effective in controlling ocular inflammation when given orally at a dose of 2 mg/kg/day in adults than when administered as intermittent intravenous pulses.
3. Most patients are treated for 1 year, and the dose is adjusted to maintain leukocyte counts between 3000 and 4000 cells/µL after the patient has been tapered off corticosteroids.
4. Inflammation control is achieved in three-fourths of patients within 12 months; disease remission occurs in two-thirds of patients within 2 years; and one-third of patients discontinue therapy within 1 year because of reversible adverse effects.

- **ADR**

1. Myelosuppression and hemorrhagic cystitis are the most common adverse effects.
2. Hemorrhagic cystitis is more common when cyclophosphamide is administered orally.
3. Patients must be encouraged to drink more than 2 liters of fluid per day while on this regimen.
4. Complete blood counts and urinalysis are monitored weekly to monthly.
5. Microscopic hematuria is a warning for the patient to increase hydration, and gross hematuria is an indication to discontinue therapy.
6. If the leukocyte count falls below 2500 cells/µL, cyclophosphamide should be discontinued until the cell count recovers.
7. Other toxicities include teratogenicity, sterility, and reversible alopecia.
8. Opportunistic infections such as Pneumocystis jirovecii pneumonia occur more commonly in patients receiving cyclophosphamide; trimethoprim-sulfamethoxazole prophylaxis is recommended for these patients.

b) Chlorambucil

- **MOA-** is a very long-acting alkylating agent that also interferes with DNA replication.
- **Indication**- Uncontrolled case series suggest that chlorambucil is effective, providing long-term, drug-free remissions in 66%–75% of patients with sympathetic ophthalmia, Behçet disease, and other sight-threatening uveitic syndromes

- **Dose, route**

1. It is absorbed well when administered orally.
2. The drug is traditionally given as a single daily dose of 0.1–0.2 mg/kg in adults.
3. It may also be administered as short-term high-dose therapy.

- **ADR**

1. Because chlorambucil is myelosuppressive, complete blood counts should be monitored closely.
2. It is also teratogenic and causes sterility.

3. Inhibitors of T-cell signaling

- **MOA**
- Cyclosporine a macrolide product of the fungus Beauveria nivea, and 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 noncalcineurin inhibitor of T-cell signaling that inhibits antibody production and B lymphocytes.

a) Cyclosporine

- **Dose**

1. Cyclosporine is available in 2 oral preparations.
2. One is a microemulsion (Neoral, Novartis, Basel, Switzerland) and has better bioavailability than the other formulation (S and immune, Novartis).These 2 formulations are not bioequivalent.
3. Neoral is initiated at 2 mg/kg/day and Sandimmune at 2.5 mg/kg/day in adults.
4. The dose is adjusted based on toxicity and clinical response to 1–5 mg/kg/day.

- **Indication**

1. Cyclosporine was shown to be effective in a randomized, controlled clinical trial for the treatment of **Behçet uveitis**, with control of inflammation in 50% of patients.
2. However, the dose used in this study was 10 mg/kg/day—substantially higher than current dosing (5 mg/kg/day)—and led to substantial nephrotoxicity.
3. Cyclosporine has also been shown to be effective in the treatment of intermediate uveitis and several types of **posterior uveitis, including VKH syndrome.**

- **ADR**

1. The most common adverse effects with cyclosporine are systemic hypertension and nephrotoxicity.
2. Additional adverse effects include paresthesia, gastrointestinal upset, fatigue, hypertrichosis, and gingival hyperplasia.
3. If serum creatinine level rises by 30%, dose adjustment is required.
4. Sustained elevation of serum creatinine levels will require a cessation of medication until levels return to baseline.
5. It is usually not necessary to monitor drug levels unless there is a concern about patient adherence or drug absorption.
6. Patients with psoriasis treated with cyclosporine appear to be at greater risk of primary skin cancers.

- **Advantage**- Overall, cyclosporine combined with corticosteroids has been shown to be modestly effective in controlling ocular inflammation (in up to 33% of patients), but toxicity necessitating cessation of therapy is more common in patients over the age of 55 years.

b) Tacrolimus

- **Dose-** is given orally at 0.10–0.15 mg/kg/day in adults.
- **ADR-** Because of its lower dose and increased potency, nephrotoxicity, is less common than with cyclosporine.
- **Advantage**

1. A prospective trial of cyclosporine and tacrolimus suggested equal efficacy in controlling chronic posterior and intermediate uveitis, with tacrolimus demonstrating greater safety (lower risk of hypertension and hyperlipidemia).
2. Long-term tolerability and efficacy are excellent as well, with an 85% chance of reducing prednisone dosage to less than 10 mg/day.

4. Biologic response modifiers

- Inflammation is driven by a complex series of cell–cell and cell–cytokine interactions.
- Inhibitors of various cytokines have been labeled biologic response modifiers.
- They play an important role in the treatment of uveitis, as these drugs result in targeted immunomodulation, thereby theoretically reducing the systemic adverse effects that are common with the previously discussed immunomodulatory drugs.

- Biologic response modifiers are considerably more expensive than traditional IMT and are reserved for specific conditions, such as Behçet disease, or situations in which traditional IMT has failed.
- TNF-α is believed to play a major role in the pathogenesis of JIA, ankylosing spondylitis, and other spondyloarthropathies.
- These drugs are generally prescribed and administered by uveitis specialists and rheumatologists experienced with their use, adverse effects, and toxicities.

a) **Etanercept**

- A TNF receptor blocker has proven effective in controlling joint inflammation in polyarticular JIA and adult rheumatoid arthritis but showed no effect in controlling active intraocular inflammation or in allowing for the taper of other immunomodulators in previously well-controlled cases.
- It is generally less effective than infliximab and is not a preferred biologic for uveitis treatment.
- There are also some reports of paradoxical inflammation with etanercept.

b) Infliximab

- **MOA-** It is a chimeric, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody directed against TNF-α,
- **Indication-** It is effective in controlling current inflammation and decreasing the likelihood of future attacks in **Behçet uveitis, idiopathic uveitis, sarcoidosis, VKH** syndrome, and many other entities in more than 75% of patients.
- **Dose, route**- It is administered through infusions.
- **Advantage**

1. It has a corticosteroid-sparing effect and appears to improve the visual prognosis of patients with recalcitrant Behçet uveitis.
2. Similar favorable effects have been reported in patients with HLA-B27–associated anterior uveitis treated with infliximab.

- **ADR**

1. However, in a recent study, although 78% of patients achieved successful control of inflammation at 10 weeks, nearly one-half could not complete the 50 weeks of therapy because of drug-induced toxicity, which included drug-induced lupus, systemic vascular thrombosis, congestive heart failure, new malignancy, demyelinating disease, and vitreous hemorrhage.
2. As many as 75% of patients receiving more than 3 infusions developed antinuclear antibodies.
3. Low-dose methotrexate (5–7.5 mg/week) may be administered concomitantly to reduce the risk of drug-induced lupus syndrome and the formation of human antichimeric antibodies, which can lead to reduced efficacy of infliximab.
4. Some patients with unknown, inactive, post-primary tuberculosis treated with infliximab subsequently developed disseminated tuberculosis. Thus, a PPD test or interferon-gamma release assay to assess for tuberculosis (TB) exposure is mandatory before starting infliximab.
5. In the case of TB exposure, treatment with TNF inhibitors may be possible with concurrent TB therapy.
6. More recent reports of infliximab suggest a lower frequency of adverse effects than that reported in earlier studies.

c) Adalimumab,

- **MOA-**It is a fully human monoclonal IgG1 antibody directed against TNF-α, has been shown to be as effective as infliximab in controlling inflammation,
- **Advantage**

1. It has success rates of up to 88% without relapse in pediatric patients with uveitis and 100% in adult patients with Behçet uveitis, posterior uveitis, and panuveitis.
2. However, uveitis relapses requiring local corticosteroid injections occurred in 42% of adult patients taking adalimumab.
3. 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.

- **Adverse effects**

1. Development of antidrug antibodies, appear to be less common than with infliximab.
2. Patients must be tested for TB exposure before starting therapy.
3. Several other TNF-α inhibitors are currently in use, including golimumab and certolizumab, but there is limited information about their utility for uveitis.

d) Rituximab

- It is a chimeric monoclonal antibody directed against CD20+ cells (mainly B lymphocytes)
- Useful in the treatment of Behçet retinal vasculitis, granulomatosis with polyangiitis– associated necrotizing scleritis, and mucous membrane pemphigoid.

e) **Anakinra**

- It 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.

f) Tocilizumab

- It 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.

g) **Intravenous immunoglobulin (IVIG)**

- It has been reported to be effective in some patients with uveitis that is otherwise refractory to immunosuppressive therapy, as well as in patients with mucous membrane pemphigoid.

h) Interferon alfa-2a/2b (IFN-α2a/b)

- **MOA-** It has antiviral, immunomodulatory, and antiangiogenic effects.
- **Indications**

1. Interferon alfa-2a/2b (IFN-α2a/b) has been reported to be beneficial in some patients with uveitis.
2. IFN-α2a seems to be an alternative to anti-TNF drugs.
3. Reports in the European literature seem to indicate that IFN-α2 a is efficacious and well tolerated in patients with Behçet uveitis, controlling inflammation in almost 90%; it is somewhat less effective in non-Behçet uveitis, with inflammation control in 60%.
4. There are also reports of IFN-α2b successfully treating uveitic CME.
5. Prior to initiation of IFN-α2a therapy, patients discontinue any other immunosuppressive drugs.

- **ADR**

1. A flulike syndrome has been observed, most frequently during the first weeks of therapy, but symptoms may be reduced through prophylactic administration of acetaminophen.
2. Despite the use of low interferon doses, leukopenia or thrombocytopenia may occur.
3. Depression is another important adverse effect of interferon therapy.