Uveitis Therapy: Paradigm and Agents

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Medical Therapy

• Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease
  • Cycloplegics
  • Non-Steroidal Anti-Inflammatory Drugs
  • Corticosteroids
  • Methotrexate

• Azathioprine
• Mycophenolate
• Alkylating agents: Cyclophosphamide and chlorambucil
• Cyclosporine
• Biologic Response Modifiers
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• **Indications**
  - Noninfectious ocular inflammatory disease
  - Other diseases in which an inflammatory component exists, if therapy directed against the primary etiology is also used (e.g., infectious disease)

• **Paradigm – Goal of Therapy**
  - Control of the inflammation
    - Eliminate the risk to vision from the structural and functional complications resulting from uncontrolled inflammation
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Paradigm – Choice of Agent
  • Based on a careful consideration of
    • Specific diagnosis
    • Concurrent ocular or systemic disease
    • Existing level of ocular function compromise
    • Monocular vs binocular disease
    • Patient desires
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Paradigm – Initial Therapy
  • The initial goal of therapy
    • Control of inflammation rapidly
  • Corticosteroids - most effective agent
    • Topically, regionally, and systemically
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Paradigm – Initial Therapy
  • Corticosteroids - most effective agent
    • The Multicenter Uveitis Steroid Treatment Trial (MUST), a randomized, controlled, superiority trial, comparing systemic anti-inflammatory therapy, versus fluocinolone acetonide implant for intermediate, posterior and panuveitis was conducted and recently published the following results
      • In each treatment group, mean visual acuity improved over 24 months, with neither approach superior, to a degree detectable with the study's power
      • The specific advantages and disadvantages identified based on individual patients' particular circumstances, should dictate selection between these two alternatives
      • Systemic therapy with aggressive use of corticosteroid-sparing immunosuppression, was well tolerated
    • For certain conditions such as mild scleritis, non-steroidal anti-inflammatory agents may be used instead of corticosteroids
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

- Certain conditions indications for the early initiation of immunomodulatory therapy
  - Strongly consider early initiation in:
    - Behçet’s with posterior segment, vision threatening involvement
    - Sympathetic ophthalmia
    - Necrotizing scleritis with systemic association
    - Serpiginous choroidopathy with vision threatening involvement
  - Some consider early initiation for other conditions such as
    - Birdshot uveitis; Juvenile Idiopathic Arthritis Associated chronic uveitis, steroid-dependent; Multifocal Choroiditis with Panuveitis; Vogt Koyanagi Harada Disease
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Tapering of Initial Therapy
  • If control of inflammation is achieved with initial therapy and disease is considered to be of acute or limited duration, then an appropriate taper of the initial agent(s) is warranted
  • If disease activity recurs with taper, then the dose of corticosteroid at which the flare occurred determines whether long-term corticosteroid therapy (baseline DEXA scan and bone preservation measures implemented) or second line therapy is used.

• If control is not achieved with initial therapy, then transition to second line therapy
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Paradigm – Second Line Therapy
  • In chronic disease not controlled at a safe dose of corticosteroid (actually, there is no chronic dose of systemic corticosteroid considered by bone specialists to be safe for chronic use)
  • acute or limited duration disease in which initial corticosteroid therapy failed to achieve control
  • individuals unable to tolerate doses of initial therapy
  • Multiple drug classes and agents - data from randomized controlled trials generally lacking
  • Selection of agent is thus based on a consideration of an individual patient’s comorbidities
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Drug Classes (as new agents are continually being developed and released, this list may be incomplete). Refer to each individual agent’s monograph for a complete discussion
  • Antimetabolites
    • Methotrexate
    • Azathioprine
    • Mycophenolate mofetil or mycophenolic acid
  • Calcineurin inhibitors
    • Cyclosporine
    • Tacrolimus
    • Sirolimus
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Alkylating agents
  • Cyclophosphamide
  • Chlorambucil

• Biological response modifiers
  • Infliximab
  • Adalimumab
  • Etanercept
  • Tocilizumab
  • Rituximab
  • Intravenous Immunoglobulin
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Paradigm – Beyond Second Line Therapy
  • If use of initial and second line therapy are ineffective in controlling inflammation
    • Considerations of the individual needs for each patient should guide choices
  • Options may include
    • Medical
      • Combination IMT - multiple drugs from more than one class of drugs
      • Surgical therapy in specific uveitic entities (i.e. therapeutic PPV in pars planitis)
Treatment guidelines utilizing systemic therapy for non-infectious ocular inflammatory disease

• Special Considerations
  • Pregnancy testing: As part of the systemic work-up, prior to initiating systemic immunosuppressive therapy, a pregnancy test should be done
  • Vaccine recommendations
    • Patients receiving anti-TNF therapy should not have live vaccines, including, but not limited to varicella zoster, oral polio, or rabies vaccination, and the influenza vaccine made with a live virus
Clinical Trials in Uveitis – NEI/NIH

• Multicenter Uveitis Steroid Treatment (MUST) Trial – RCT, Open label,
  • Compare standard systemic therapy to fluocinolone implant – outcomes, complications
• Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study – Retrospective
  • Specific therapies, complications, and cancer mortality
NIH funded RCT that asked: Which is better for treatment of chronic non-infectious uveitis?

- Systemic therapy (steroids + IMT) - better visual outcomes at 7 years (7 letter gain) compared to Fluocinolone implant with comparable QOL and safety data.

Do Immunosuppressive agents increase risk of cancer mortality? SITE

- Azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, systemic corticosteroids, or dapsone had overall cancer incidence rates and cancer mortality similar to that of patients who never took immunosuppressive drugs.

- Cyclophosphamide, overall mortality was not increased and cancer mortality was non-significantly increased.

- Tumor necrosis factor inhibitors were associated with increased overall risk (adjusted hazard ratio [HR] 1.99, 95% CI 1.00 to 3.98) and cancer mortality.

Cycloplegics

• Indications
  • Anterior chamber involvement in uveitis
    • To prevent formation of new posterior synechiae with either continual or intermittent dilation
    • To decrease photophobia and pain due to ciliary and sphincter muscle spasm
    • To break recently formed posterior synechiae

• Contraindications
  • Allergy or sensitivity to agent or to others in its class

• Pre-procedure/therapy evaluation
  • Check angle depth because of possibility of inducing narrow-angle glaucoma
Cycloplegics

- Dosage (agents listed in decreasing order of duration of effect)
  - The dosages are adjusted according to desired duration
    - Atropine 1% one to 4 times daily (severe cases-hypopyon). The higher dose should be used with caution in young children.
    - Scopolamine 0.25% one to four times daily
    - Homatropine 2% or 5% one to four times daily
    - Cyclopentolate 1% one to four times daily
    - Tropicamide 0.5% to 1% for prophylactic nightly dilation
  - Most effective use to prevent new synechiae requires monitoring of pupil size and shape by the patient
Cycloplegics

• Complications
  • Psychosis (esp. Atropine)
    • pediatric age group, older adults
  • Tachycardia
  • Fever
  • Urinary retention
Cycloplegics

- Cycloplegia/blurred vision
  - Can be minimized by use of a short acting cycloplegic with bedtime regimen
  - Temporary use of reading glasses
- Posterior synechiae formation in the dilated position can be minimized by prescribing strong cycloplegics only with adequate anti-inflammatory treatment
- **Atropine may cause a widely dilated pupil that is “fixed” due to posterior synechiae**
Which of the following agents is associated with the longest duration of pharmacological dilation of the pupil (on average)?

• Tropicamide 1%
• Scopolamine 0.25%
• Cyclopentolate 2%
• Homatropine 5%
Cycloplegic induced psychosis is most likely to occur in which age group?

- Pediatric
- Young adult
- Elderly
- Late teens
Non-Steroidal Anti-Inflammatory Drugs (NSAID)

• Indications
  • Scleritis/episcleritis
    • Topical NSAIDs may be of benefit in episcleritis only
  • Maybe useful as a steroid-sparing adjunct during tapering of topical corticosteroids in selected cases of JIA/JRA and HLA-B27-associated iridocyclitis
  • Cystoid macular edema (CME)
    • Topical NSAIDs
  • Analgesia
Non-Steroidal Anti-Inflammatory Drugs (NSAID)

• Contraindications
  • Renal insufficiency or other kidney disease
  • Allergy or sensitivity to agent or others in its class
  • Peptic ulcer disease
  • Bleeding diathesis
  • Use of COX inhibitors with an established history or risk factors for cardiovascular or thrombotic disease
Non-Steroidal Anti-Inflammatory Drugs (NSAID)

• Complications
  • Oral
    • Renal insufficiency
    • Gastritis/peptic ulcer – especially when used with systemic corticosteroids
    • Nausea
    • Decreased clotting ability
    • Abnormal liver enzymes
Non-Steroidal Anti-Inflammatory Drugs (NSAID)

- Topical
  - Corneal epithelial breakdown, thinning, erosion, ulceration, perforation
    - Do not exceed recommended frequency of use
  - Ocular wound healing delay
  - Ocular bleeding
  - Conjunctival hyperemia
Which of the following is most likely to induce peptic ulcers?

- Systemic corticosteroids
- Systemic nonsteroidal anti-inflammatory drugs (NSAIDS)
- Systemic corticosteroids combined with NSAIDS
- All are equally likely to cause peptic ulcers
Corticosteroids

• Indications
  • Noninfectious ocular inflammatory disease
  • Infectious uveitis (as adjunctive therapy in combination with antimicrobials)
  • Other diseases in which an inflammatory component exists, if therapy directed against the primary etiology is also used (e.g., infectious disease)
Corticosteroids

• Contraindications
  • Infectious etiology, unless covered by appropriate antibiotics
  • Poorly controlled or difficult to control diabetes
  • Peptic ulcer or erosive gastritis
  • Concomitant oral NSAIDS
  • A relative contraindication is a history of corticosteroid-induced intraocular pressure (IOP) elevation
Corticosteroids

• Topical Preparations
  • Difluprednate 0.05% (Durezol)
  • Prednisolone acetate 1% (Pred Forte), 1/8% (Pred Mild)
  • Loteprednol etabonate 0.5% (suspension, gel and ointment) (Lotemax)
  • Prednisolone sodium phosphate 1% (Inflamase)
  • Fluorometholone 0.1% (FML)
  • Dexamethasone sodium phosphate 0.1% (Decadron)
  • Rimexalane 1% (Vexol)
Corticosteroids

• Uveitis Therapeutics – Local
  • Regional: Periocular – retroseptal or posterior sub-Tenon injection
    • Corticosteroids
      • Triamcinolone 10-40mg
  • Intraocular
    • Corticosteroids
      • Triamcinolone 4mg/0.1cc
    • Antibiotics
    • VEGF inhibitors – Avastin 1.25mg/0.05ml
Corticosteroids

• Periocular Preparations and Potencies (relative anti-inflammatory activity compared to hydrocortisone)
  • Long-acting
    • Methylprednisolone acetate (DepoMedrol) (5.0)
    • Triamcinolone acetonide (Kenalog) (5.0)
    • Triamcinolone diacetate (Aristocort) (5.0)
  • Short-acting
    • Hydrocortisone sodium succinate (Solu-Cortef) (1.0)
    • Betamethasone (Celestone) (25)
Corticosteroids

• Regional
  • Sub-Tenon’s, retroseptal/orbital floor, sub-conjunctival, intraocular
    • Triamcinolone acetonide 40 mg/ml, up to 1ml
    • Methylprednisolone acetate 40 mg/ml or 80 mg/ml, up to 1 ml
    • Betamethasone sodium phosphate/betamethasone acetate, 6 mg/ml, up to 1 ml
      (combination depot and immediate action formulation (must be given with lidocaine roughly 1:10)
    • Dexamethasone phosphate 4mg/ml (must be given with lidocaine roughly 1:10)
    • Fluocinolone acetonide 0.19 mg (Iluvien) an injectable corticosteroid implant
    • Fluocinolone acetonide 0.59 mg intravitreal implant (elutes corticosteroid medication into the eye for up to 3 years). It requires a surgery for implantation, and is secured with partial thickness scleral sutures
    • Dexamethasone 0.7 mg injectable corticosteroid implant with extended drug release, it is a continuous release for 35 days, then it biodegrades
Corticosteroids

Posterior Subtenon Triamcinolone Injection

Photograph courtesy of Ramana S. Moorthy MD.
Corticosteroids

Inferior Retroseptal Triamcinolone Injection

Photograph courtesy of Ramana S. Moorthy MD.
Corticosteroids

• Agents commonly used in the U.S.
  • Oral
    • Prednisone 1 mg/kg/day
    • Prednisolone 1 mg/kg/day
    • Dexamethasone 0.2 mg/kg/day
  • Intravenous
    • Methylprednisolone 1 gm/day, typically for 3 days total
    • Dexamethasone 200 mg/day x 3 days
Corticosteroids

• Ocular Complications - for all forms
  • Posterior subcapsular cataracts (not reversible),
  • Increased intraocular pressure (IOP) (often reversible)
Corticosteroids

• Complications - Systemic Use
  • Short term
    • Weight gain
    • Mood effects, sleep disturbance and psychosis
    • Acute hyperglycemia
    • Manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in persons with diabetes
    • Exacerbation of hypertension, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, and hypertension
Corticosteroids

- Aseptic necrosis of femoral and humeral heads (Dosages over 60mg/day associated with greater risk of aseptic necrosis of the femoral head)
- Menstrual irregularities
- Urticaria and other allergic, anaphylactic or hypersensitivity reactions
- Infection, reduced symptoms from infection
- Increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, headache, insomnia, emotional disturbances
Corticosteroids

• Long term
  • Osteoporosis, osteopenia (this begins by 3 months of steroid therapy)
  • Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, striae and may suppress reactions to intradermal skin tests (e.g., purified protein derivative test for tuberculosis infection)
  • Pancreatitis; abdominal distention; ulcerative esophagitis; increases in alanine transaminase, aspartate transaminase and alkaline phosphatase have been observed following corticosteroid treatment ("fatty liver"). In most cases, side effects are minor, not associated with any clinical syndrome and are reversible upon discontinuation; peptic ulcer with possible perforation and hemorrhage (risk appears to be associated primarily with concurrent use of non-steroidal anti-inflammatory drugs)
Corticosteroids

- Reactivation of latent tuberculosis
- Pathologic fracture of long bones, muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures
- Fat redistribution, adrenal suppression, accelerated atherosclerosis, development of Cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth of children; decreased carbohydrate tolerance
Corticosteroids

• Complications - Regional use
  • Injection into choroidal or retinal circulation or emboli
  • Perforation of globe with permanent loss of vision
  • Ptosis (more common with superior injections)
  • Proptosis
Corticosteroids

- Orbital fat prolapse (with inferior retroseptal injections)
- Delayed hypersensitivity reactions
- Subconjunctival hemorrhage
- Chemosis
- Infection
- Pain from injection, syncope, scarring, Cushing Syndrome, pupillary dilation
Corticosteroids

• Complications - Intravitreal corticosteroid implants
  • Surgical complications
    • Approximately 100% of phakic patients will need cataract surgery at 2 years (sustained release implants)
    • Approximately 40% will need surgical intervention for glaucoma at 2 years, approximately 50% will need topical medication for glaucoma at 3 years (sustained release implants)
    • Vitreous opacities
    • Vitreous hemorrhage
Corticosteroids

- **Rare complications**
  - Late spontaneous dissociation of the implant from the anchoring strut
  - Conjunctival erosion of anchor suture with a high risk for endophthalmitis

- **Perioperative management**
  - Maintenance of optimal immunomodulatory therapies preoperatively
  - Begin tapering concomitant immunomodulatory therapy when clinically optimal post-operatively
  - Monitor carefully for intraocular pressure rise and treat aggressively with MMT; engage glaucoma specialist early to manage and intervene surgically when appropriate to prevent irreversible optic nerve damage
  - Monitor cataract progression and intervene surgically when inflammatory status is stable and cataract is visually significant
Corticosteroids

• Complications - Topical use
  • Worsening of external infectious disease
  • Increased incidence and frequency of spontaneous subconjunctival hemorrhages
Corticosteroids

• Follow-up care
  • Systemic use
    • Routine monitoring of blood pressure, weight, and response to therapy may vary, but generally every 4-6 weeks
    • Long-term use should be avoided
    • If long term therapy cannot be avoided, monitor bone mineral density initially, then approximately yearly, as well as cholesterol and lipids, and embark upon bone preservation strategies
  • Topical, regional, intravitreal use
    • Monitor IOP and cataract status
If a patient was treated with prednisone 60 mg daily for 1 week for uveitis, and the prednisone dose was tapered and discontinued over a 6 week period thereafter, which of the following complications of corticosteroid therapy would be least likely to occur during the period of treatment?

• Weight gain
• Aseptic necrosis of the hip
• Hypertension
• Mood disturbances
The following tests need to be performed for patients on maintenance doses of oral prednisone of <10mg per day

• Monthly SGOT/SGPT (AST/ALT)
• Monthly BUN / Creatinine
• Annual Complete blood count
• Annual bone density scan
# Antimetabolites and Alkylating Agents

<table>
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<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Dosage/Route</th>
<th>Potential Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
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</tr>
<tr>
<td>Methotrexate</td>
<td>Increases extracellular adenosine</td>
<td>7.5–25.0 mg/wk PO, SQ</td>
<td>GI upset, fatigue, hepatotoxicity, pneumonitis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Alters purine metabolism</td>
<td>100–250 mg/day PO</td>
<td>GI upset, hepatotoxicity</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits purine synthesis</td>
<td>1–3 gm/day PO</td>
<td>Diarrhea, nausea, GI ulceration</td>
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<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cross-links DNA</td>
<td>1–2 mg/day PO</td>
<td>Hemorrhagic cystitis, sterility, increased risk of malignancy</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Cross-links DNA</td>
<td>2–12 mg/day PO</td>
<td>Sterility, increased risk of malignancy</td>
</tr>
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</table>
Immunomodulatory Therapy

• First line therapy
  • Sulfones – Milder OCP
    • Sulfasalazine, sulfapyridine
    • Dapsone
  • Corticosteroids in most cases
Immunomodulatory Therapy

• Second line therapy - TRADITIONAL
  • If corticosteroids fail
    • Fail to achieve inflammatory control at reasonable maintenance doses
    • Fail because they are not tolerated
  • Anti-metabolites
  • Calcineurin Inhibitors
  • Alkylating agents –
    • Necrotizing scleritis and PUK – Systemic Vaculitis
    • OCP – rapidly progressive
  • Combinations of agents in different classes at lower doses
• SITE- Systemic Immunosuppressive Therapy for Eye Diseases Studies
Immunomodulatory Therapy

• Third line therapy
  • Biolgic Response Modifiers
    • Anti-TNF alpha therapy
      • Infliximab
      • Adalimumab
    • Anti-CD 20 – B cell destructions
      • Rituximab
    • OTHERS
  • IV Immunoglobulin therapy
Immunomodulatory Therapy: Mechanism of Action – Inhibit T-cell Replication

Immunomodulatory Therapy Monitoring

• Baseline
  • CBC with differential and Platelets
  • LFTs
  • Complete Metabolic Panel (CMP) – Creatinine- with CyA and Tacrolimus
  • TPMT activity – if Azathioprine

• Routine Monitoring
  • CBC, LFTs –
  • CMP – Creatinine- with CyA and Tacrolimus
  • Initially monthly
    • When stable dose :
      • Every 2-3months
Immunomodulatory Therapy
Special Considerations – Fetal Risk

- **MINIMAL FETAL OR MATERNAL RISK**
  - Hydroxychloroquine
  - Sulfasalazine

- **SELECTIVE USE ALLOWED DURING PREGNANCY**
  - NSAIDs and aspirin
  - Glucocorticoids
  - Azathioprine and 6-MP
  - TNF inhibitors
  - Intravenous immune globulin
  - Cyclosporine
  - Tacrolimus

- **MODERATE TO HIGH RISK OF FETAL HARM**
  - Cyclophosphamide
  - Methotrexate
  - Mycophenolate mofetil
  - Leflunomide
  - Third trimester use of NSAIDs and aspirin

- **UNKNOWN RISK**
  - Anakinra
  - Rituximab
  - Abatacept
  - Tocilizumab
Anti-Metabolites
Methotrexate
Anti-Metabolites - Methotrexate

- Pharmacokinetics
  - Subcutaneous injection - greater bioavailability and reduced gastrointestinal side effects than oral
  - Onset of action – slow- up to 3 to 6 months for full intraocular effect
- Dosage
  - Maximum dosage in the range of 15 mg to 25 mg/week
  - Pediatric dosing 5-15 mg/m2
- Level II-2 evidence for Ocular Inflammatory Diseases (OID)
  - SITE – 66% -no inflammation in 1 year and 58% reduced Pred <10mg/d

Anti-Metabolites - Methotrexate

• Complications
  • **NO long term increase risk of Neoplasia**
  • Leukopenia
  • **Elevation of liver enzymes** - Cirrhosis
  • Pulmonary fibrosis

• Prevention of complications
  • Use of *folic acid* 1-2 mg/day usually decreases severity of side effects.
  • *Alcohol abstinence* to obviate additive hepatotoxicity
  • Avoidance of other medications which affect liver
  • *Appropriate contraception* for women of childbearing age for at least 3 months after discontinuing the medication
  • Potential for sperm mutation: 4 months off drug for males prior to attempting conception
Anti-Metabolites

Azathioprine
Anti-Metabolites
Azathioprine

- Pre-therapy evaluation
  - Test for inherited thiopurine methyltransferase (TPMT) deficiency
    - 89% wild type; 11% heterozygous; 0.3% homozygous
- Dosage
  - 1 – 3.0 mg/kg/day (100-200mg/day typical dose)
  - Reduced dose for Heterozygous TPMT deficiency
- Level II-2 evidence in OID
  - SITE – 62% -no inflammation in 1 year and 47% reduced Pred <10mg/d

Anti-Metabolites
Azathioprine

• Complications
  • Nausea, Headache
  • Leukopenia
    • Potentially rapid bone marrow suppression if homozygous TPMT mutation
  • Elevation of liver enzymes
  • Possible increased long-term risk of malignancy (lymphoma, leukemia)
Anti-Metabolite - Mycophenolate Mofetil
Anti-Metabolite
Mycophenolate Mofetil

• Dosage
  • 1000 to 1500 mg twice daily

■ Complications
  • Gastrointestinal (GI) disturbance – 18%
  • Leukopenia, pure red cell aplasia (PRCA)
  • Possible increased long-term risk of malignancy (lymphoma, leukemia),
  • Progressive multifocal leukoencephalopathy

• Level II-2 evidence for use in OID
  • SITE – 73% -no inflammation in 1 year and 55% reduced Pred <10mg/d
  • Level 1 evidence for rejection prevention in organ transplantation

Calcineurin Inhibitors
Cyclosporine and Tacrolimus
Calcineurin Inhibitors
Cyclosporine and Tacrolimus

• Dosage
  • 2.0 to 5 mg/kg/day, typically in two divided doses with adjustment depending on clinical response and toxicity
    • USP modified cyclosporine is typically 4.0 mg/kg/day
    • Unmodified cyclosporine A is typically 5 mg/kg/day
  • Tacrolimus – 0.1-0.15mg/kg/day

• Level II-2 evidence for OID (Behçet)
  • SITE – 52% -no inflammation in 1 year and 36% reduced Pred <10mg/d
  • LEVEL 1 evidence for rejection prevention in organ transplantation

Calcineurin Inhibitors
Cyclosporine and Tacrolimus

• Complications
  • Hypertension
  • Reduction in estimated creatinine clearance
  • Hirsutism
  • Gingival hyperplasia
  • Trembling and shaking of hands/paresthesia
  • Acne or oily skin
Alkylating Agents

Cyclophosphamide

Mechanism of Action:

- Glutathione S-transferase
- Inactive metabolites
- DNA repair
- Protein damage (apoptosis)
- DNA Crosslinking and cell death
Alkylating Agents
Cyclophosphamide

• Dosage
  
  • Cyclophosphamide
    
    • **ORAL** 100-150 mg/day typical initial dose increased to a maximum 200mg/day if uveitis remains active
    
    • **IV pulse** – 500-1000mg IV q monthly for 6-12 months
    
    • Target leukocyte count 3,000-4,000 cells/µl off steroids
    
    • Maximum cumulative cyclophosphamide dose 35gm before risk of secondary leukemia substantially increases
  
  • Level II-1 evidence of efficacy in OCP, I and II-1 systemic vasculitis
    
    • **SITE** – 76% -no inflammation in 1 year and 61% reduced Pred <10mg/d

*Foster CS. Tran Am Ophthalmol Soc. 84:527-663. 1986*

Alkylating Agents

Chlorambucil

Mechanism of Action:
- Aromatic Alkylating Agent
- Similar to Cyclophosphamide –
  Cross linking of DNA and inhibition of DNA replication
- Longer duration of effect
- Short term high dose and long term low dose therapy

Alkylating Agents: Cyclophosphamide and Chlorambucil

• Complications

  • Leukopenia or bone marrow suppression
  • Opportunistic Infection
    • Pneumocystis carinii prophylaxis
      • Trimethoprim-sulfamethoxazole, one tablet, single strength, daily
  • Hemorrhagic cystitis – (Cyclophosphamide) – Acrolein increases risk of subsequent bladder cancer
  • Gonadal suppression and permanent infertility
  • Pulmonary fibrosis
  • Neoplasia – Leukemia and lymphoma
Biologic Response Modifier

• Most uveitis specialists would not manage the administration of these agents but would refer the patient to a rheumatologist.
• Note that these agents are considered off label for ocular disease.
• Must be sure that inflammation is non-infectious.
• The role of these medications in transplantation is unknown.
BIOLOGIC RESPONSE MODIFIERS

- **Ligand blockade**
  - TNF-α
  - INF-α
  - Anti-CD3

- **Receptor blockade**
  - IL-6
  - IL-6R
  - gp130

- **Receptor downregulation**
  - αLβ2 integrin

- **Depletion**
  - CD20

- **Signalling induction**
  - TCR-CD3 complex

Drugs:
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab pegol
- Canakinumab
- Briakinumab
- Ustekinumab
- Omalizumab
- Belimumab
- Eculizumab
- Mepolizumab
- Reslizumab
- Etanercept
- Atacicept
- Alefacept

Other mouse monoclonal antibodies include:
- Tocilizumab
- Eralizumab
- Natalizumab
- Vedolizumab
- Abatacept

- Efalizumab
- Omalizumab
- Otelixizumab
- Teplizumab
- Epratuzumab

- Rituximab
- Ofatumumab
- Ocrelizumab
- GA101
- Alemtuzumab
- Muromonab
- Epratuzumab

- Otelixizumab
- Teplizumab
- Muromonab
- GA101
- Infliximab
- Adalimumab
- Rituximab

*Note: Some drugs are indicated with an asterisk.*
Biologic Response Modifiers

• Rationale for Use in OID
  • Clinical trials – Rheumatology and More Recently Ophthalmology
  • Dosing, duration of therapy, and agent choice
    • Empiric
Immunology of TNF-α

- CD4+ T cell
- Anti-inflammatory cytokines (IL-10, IL-1Ra, soluble TNFR, IL-11)
- Bone and cartilage destruction
- Pro-inflammatory cytokines (such as IL-6, IL-8, GM-CSF)
- IL-1
- Signals
- Macrophage
- TNF

Nature Reviews Immunology
TNF-α Inhibitors
TNF-α Inhibitors

- Etanercept (Enbrel®)
  - LEVEL I - no better than placebo for the treatment of uveitis
- Infliximab (Remicade®) – IV infusions
  - LEVEL II-1, II-2 - approved in Japan/EU for the treatment of patients with Behcet’s Disease and associated uveitis
- Adalimumab (Humira®) – SQ Injections
  - Level I, II-2 and III evidence – efficacy in treatment of uveitis
- Certolizumab (Cimzia®) (pegylated Fab) – Level III evidence
- Golimumab (Simponi®) – Level III evidence
TNF-α Inhibitors

• Complications
  • TNF alpha inhibitors
    • Infusion reactions other than hypersensitivity reactions
    • Hypersensitivity reactions
    • Exacerbation of demyelinating disease
    • Congestive heart failure
    • Exacerbation of tuberculosis and other latent infections (e.g., histoplasmosis)
    • Drug induced lupus
    • Neoplasia (acute leukemia, infliximab)
    • Production of neutralizing antibodies
    • De novo uveitis (etanercept)
Adalimumab: Humira™: Visual I & II

Visual I and II studies

- Compared to tapering doses of oral corticosteroids,
- Adalimumab increases the interval to treatment failure from 13 weeks to 24 weeks,
- Adalimumab increases the interval to flare from 4.8 months to 10 months.
- Adalimumab Reduces risk of visual acuity loss.

Adalimumab FDA approved in 2016 for noninfectious intermediate uveitis, posterior uveitis, and panuveitis

Primary endpoint: Time to treatment failure*

- Hazard ratio for time to treatment failure between ADA and PBO is 0.5 (0.36–0.70), p<0.001, therefore, the risk to fail was reduced by 50% for ADA compared with PBO.
- The median time to treatment failure was prolonged by 87% from 13 weeks for placebo to 24 weeks for ADA.

*ITT population

2. Brezov A. et al, SOE 2015, Oral Presentation FP-UVE0065
Components of Primary Endpoint, Time to Treatment Failure*

- Adalimumab significantly reduced worsening of AC cell grade, VH cell grade, BCVA and reduced development of new lesions

*ITT population

Brezin A. et al, SOE 2015, Oral Presentation FP-UVE-0065
Primary endpoint: Time to treatment failure*

- Hazard ratio for time to treatment failure between ADA and PBO is 0.57 (0.39–0.84), p=0.004, therefore, the risk to fail was reduced by 43% for ADA compared with PBO.
- The median time to treatment failure was 8.3 months for PBO, but was not estimable for ADA, as fewer than half of the ADA-treated patients experienced treatment failure.

*ITT population

The effect of adalimumab on the risk of treatment failure compared to placebo

**VISUAL I**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=107)</th>
<th>ADA (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to treatment failure</td>
<td>3.0 months</td>
<td>5.6 months</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.50</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>95% CI for HR</td>
<td>(0.36, 0.70)</td>
<td></td>
</tr>
</tbody>
</table>

**VISUAL II**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=111)</th>
<th>ADA (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to treatment failure</td>
<td>8.3 months</td>
<td><em>(&gt;18 months)</em></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.57</td>
<td>p= 0.004</td>
</tr>
<tr>
<td>95% CI for HR</td>
<td>(0.39, 0.84)</td>
<td></td>
</tr>
</tbody>
</table>

*The median time to treatment failure was 8.3 months for PBO, but was not estimable for ADA, as fewer than half of the ADA-treated patients experienced treatment failure. However, median time is >18 months since the median was still not reached by end of study at 18 months.*

Conclusions

- In patients with active, non-infectious uveitis uncontrolled with prednisone ≥10 mg daily, ADA significantly lowered the risk for uveitic flare or BCVA loss.

- Patients on ADA had a lower risk to fail and fewer criteria of treatment failure were met.

- Worsening of AC cell grade, VH grade, and BCVA from best state achieved, as well as occurrence of new lesions were reduced with ADA compared with placebo.

- Adverse event data were similar between the ADA and placebo groups. The safety profile was consistent with the known safety profile of ADA across approved indications.
Conclusions

• In steroid-dependent patients with inactive, non-infectious uveitis, ADA lowered the risk for uveitic flare or vision loss

• Patients on ADA had a lower risk to experience TF and fewer criteria of TF were met

• Secondary endpoints were numerically in favor of ADA, although significant differences between ADA and PBO were not observed

• Adverse events were similar between the ADA and PBO groups. The safety profile was consistent with the known safety profile of ADA across approved indications and this population. No new safety signals were identified

Rituximab

Anti-CD20 monoclonal antibody chimeric monoclonal antibody directed against CD20-positive B-lymphocytes. B-cell Apoptosis
Rituximab

- Level and I and II-1 evidence of efficacy in
  - Refractory Scleritis
  - Systemic vasculitides (GPA)
  - OCP
  - Pediatric uveitis
  - Orbital inflammation

Rituximab

Complications
• Profound Lymphopenia
• Hypersensitivity reactions
• Infusion reactions – Fevers, Nausea
Which of the following immunosuppressive agents used to treat ocular inflammatory disease is most clearly associated with an increased risk of malignancy?

• Cyclosporine
• Azathioprine
• Methotrexate
• Cyclophosphamide
The daily dosage of cyclosporine should be adjusted based on which of the following laboratory tests?

• Hematocrit
• Platelet count
• Creatinine
• Glucose
What does the monoclonal antibody Infliximab (Remicade) target?

• Interleukin-2
• Cyclo-oxygenase 2
• Choroidal melanoma cells
• Tumor necrosis factor-alpha
Which of the following is not a contraindication to tumor necrosis factor inhibitors?

• Multiple sclerosis
• Uveitis in a child younger than 10-years-old
• Tuberculosis
• Heart failure
The most common side effect of mycophenolate mofetil is

• Gastrointestinal disturbances – diarrhea
• Myelosuppression
• Elevation of liver function tests
• Nephrotoxicity
Which anti-metabolite has the most rapid onset of therapeutic immunosuppressive activity?

- Methotrexate
- Chlorambucil
- Mycophenolate mofetil
- Azathioprine
Biologic Response Modifiers

• Cytokine receptor blockade
  • Abatacept (Orencia)— useful in refractory JIA uveitis
    • Soluble fusion protein CTLA-4+Fc IgG1 fragment
    • Binds CD80/CD86 ; binds B7 on antigen presenting cells, effectively preventing binding of the APC to T-lymphocytes and preventing T cell activation
    • Blocks the CD28 costimulatory signal and inhibits T-cell activation.

• Interferons : Recombinant human cytokine/cytokine analogues
  • Mechanism of action of the interferons is poorly understood
  • antiviral, antineoplastic, and antiangiogenic effects
  • Treat mucocutaneous, articular, and ocular Behçet Disease
Th-Cell Subsets and Functions

- **Th1** (T-bet): IL12 → IFNγ → CTL → Cellular immunity
- **Th2** (GATA-3): IL4 → IL4, IL5, IL13 → B → Humoral immunity
- **Th17** (RORγt): IL17A/F, IL21, IL22 → Eosinophil, PMN → Autoimmunity, Extracellular bacterial, Fungi

Xu S, Cao X. Cellular & Molecular Immunology (2010) 7, 164–174; doi:10.1038/cmi.2010.21; published online 19 April 2010
Biological Activities of IL-17

Xu S, Cao X. Cellular & Molecular Immunology (2010) 7, 164–174; doi:10.1038/cmi.2010.21; published online 19 April 2010
Biologic Response Modifiers : Emerging Therapies

• Secukinumab
  • Fully humanized antibody to IL17 A
  • 2 infusions 3 weeks apart
  • sustained anti-inflammatory activity for 2 months
Summary

• Follow Treatment Paradigm
• Early Institution of Immunomodulatory Therapy for the Most Severe Diseases
• Therapy requires vigilance and laboratory monitoring
• Therapy may be required for years
Necrotizing Scleritis
Acute Anterior Uveitis – HLAB27+
Acute Anterior Uveitis

• Frequent topical steroids tapered slowly over 3-4 months with topical cycloplegics
• Periocular steroid injections
• Oral corticosteroids
• Recurrent disease
• Chronic Disease
Chronic anterior uveitis

• Underlying systemic diseases: Children – JIA, Adults – Idiopathic, sarcoid
• Topical steroids and cycloplegics
• IMT
• Anti-TNF therapy
Diagnosis and Treatment

Photograph courtesy of Ramana S. Moorthy MD
Birdshot Uveitis

- Oral steroids, Intravitreal Retisert implant
- Long term IMT – Cellcept, Imuran, MTX, anti-TNF agents (Humira)
Diagnosis?
Sarcoid Uveitis

- Steroid sensitive
  - Topical, regional and systemic corticosteroids
Diagnosis?
Behçet Disease

- Retinal Vasculitis
  - Anti-TNF therapy – Remicade
    - Works faster than steroids

- Recurrent anterior uveitis and chronic panuveitis
  - Topical, regional, and oral steroids
  - Long term IMT – Imuran, cellcept
Diagnosis
Necrotizing Herpetic Retinitis

Etiology: PCR of aqueous
Therapy: Systemic anti-virals then added oral steroids (avoid steroids in AIDS)
Diagnosis?
CMV Retinitis

• Etiology: Aqueous PCR
  • HIV
  • Iatrogenic immunocompromise

• Therapy:
  • IV and Intravitreal Antivirals -
    • Until immune reconstitution
  • Avoid systemic and regional steroids