Regional vs. Systemic Therapy for Uveitis

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Corticosteroids

- Mainstay of initial treatment
- Inhibit production of cytokines that initiate the inflammatory cascade
- Potent
- Rapid onset of action
- Systemic: oral, intravenous
- Regional therapy: topical, injections, implants

Regional vs. Systemic Therapy

- Considerations
  - Anatomic location of inflammation
  - Unilateral vs. bilateral
  - Course – acute, recurrent or chronic
  - Systemic involvement
  - Efficacy
  - Safety
  - Tolerability
  - Individual preference

Corticosteroids

- Mainstay of initial treatment
- Inhibit production of cytokines that initiate the inflammatory cascade
- Potent
- Rapid onset of action
- Systemic: oral, intravenous
- Regional therapy: topical, injections, implants
Corticosteroids: Adverse Effects

- Ocular: cataracts, glaucoma
- Systemic: Cushingoid changes, bruising, impaired wound healing, osteopenia, osteoporosis, GI bleeding, infection, mood changes, myopathy, growth suppression, pancreatitis, avascular necrosis, hypertension, diabetes

Systemic Immunomodulatory Therapies

- Antimetabolites
  - methotrexate, mycophenolate mofetil, azathioprine
- T cell inhibitors
  - cyclosporine, tacrolimus, sirolimus
- Alkylating agents
  - cyclophosphamide, chlorambucil
- Biologics
  - infliximab, adalimumab, rituximab

Regional Therapy

- Topical
  - corticosteroid drops
- Periocular
  - triamcinolone acetonide
- Intravitreal
  - triamcinolone acetonide, anti-VEGF agents, methotrexate, infliximab
- Implants
  - fluocinolone acetonide, dexamethasone
**Anatomical location of inflammation**

- **Anterior**
- **Intermediate**
- **Posterior**
- **Panuveitis**

**Clinical Course of Uveitis**

**TABLE 2. The SUN* Working Group Descriptions of Uveitis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Insidious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited</td>
<td>≤3 months duration</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
<td>&gt;3 months duration</td>
</tr>
<tr>
<td>Course</td>
<td>Acute</td>
<td>Episodes characterized by sudden onset and limited duration</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Repeated episodes separated by periods of remission without treatment ≤3 months in duration</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Persistent uveitis with relapse in ≤3 months after discontinuing treatment</td>
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*SUN = Standardization of uveitis nomenclature.

**Anterior uveitis**

- Majority of uveitis cases
- 70% in Northern California population-based study
- Typically can be treated with topical corticosteroids or periocular injections
- Most cases are acute or recurrent
- If chronic, long-term low dose topical steroids may be used

**How much topical corticosteroid is acceptable chronically?**

- No definitive answer
- Current thinking
  - American Uveitis Society survey 2009:
    - Most prefer prednisolone acetate ≤2 drops a day
  - Thorne et al, *Ophthalmol* 2010
    - In JIA, ≤3 drops daily of topical corticosteroid was associated with a 87% lower risk of cataract development compared to those eyes treated with >3 drops daily (relative risk = 0.13, 95% CI: 0.02, 0.69, P = 0.017)
When is systemic therapy indicated?

- When inflammation can not be chronically controlled on a low dose of topical steroids
- Intolerance or side effects with steroids
- Systemic disease
  - HLA-B27 disease with axial involvement
  - Sarcoidosis
  - Juvenile arthritis

Intermediate uveitis

- Some patients may require intermittent or no treatment
- Decision to treat based on vision, vitreous haze and structural complications

Pars Planitis: A 20-Year Study of Incidence, Clinical Features, and Outcomes

- Long-term population based study (Olmstead County)
- 30/46 patients required treatment
  - Topical steroids 43.5%
  - Periocular steroids 41.3%
  - Systemic steroids 23.9%
  - Steroid sparing therapy 1/46
  - Vitrectomy 2/46 (1 ERM, 1 severe vitritis)
How did patients do?

- Visual prognosis of pars planitis is relatively good
- 75% of patients maintained a visual acuity of 20/40 or better after 10 years

When to consider an implant or systemic steroid-sparing therapy

- Worsening of disease when oral steroids are tapered or when injections wear off
  - CME
  - Vasculitis
  - Neovascularization
  - Increased vitreous haze

Posterior/Panuveitis

- Topical corticosteroids do not penetrate
- Regional injections may be acceptable for acute or recurrent disease
**Corticosteroid injections**

- Posterior subtenons or orbital floor
  - typically 1 cc (40 mg) triamcinolone acetonide
- Intravitreal
  - 0.1 cc triamcinolone acetonide
  - Available in a preservative-free formulation

**Intravitreal corticosteroids**

- Largest study (Kok, Lightman et al, *Ophthaimol* 2005) of 65 eyes (54 patients)
  - Mean follow-up 8 months
  - 83% had improvement in CME and visual acuity
  - Mean VA gain (12 letters)
  - 43% had an IOP rise of > 10 mm Hg; 51% required medical therapy
  - No glaucoma surgeries and no loss of VA due to IOP

**Johns Hopkins study of 156 eyes (126 patients) treated with 1 PST**

- 53% had resolution of CME at 1 month
- 57% had resolution at 3 months
- 57% had 3-line improvement in visual acuity at 3 months
- 19% had IOP > 30 mm Hg (0.14/eye-year)
- 10% developed new cataract (0.13/eye-year)
- 14% developed ptosis (0.09/eye-year)

Data courtesy of J. Thorne and A. Leder

**Why are injections problematic for chronic diseases such as serpiginous choroidopathy, birdshot, sympathetic ophthalmia, etc?**
When should you think about steroid-sparing systemic therapy or an implant?
- Chronically requires > 10 mg prednisone
- Steroid side effects
- Known chronic diseases
  - Behçets with posterior segment involvement
  - Ocular cicatricial pemphigoid
  - Necrotizing scleritis
  - Birdshot chorioretinopathy
  - Multifocal choroiditis with panuveitis
  - Serpiginous choroidopathy
  - Sympathetic ophthalmia

Sustained release corticosteroid implants
- Fluocinolone acetonide (Retisert)
  - FDA-approved for uveitis
  - 30 months of therapeutic drug delivery
  - 0.3-0.4 micrograms/day over 30 months
  - Callanan et al, Archives 2008:
    - Pre-implant recurrence rate 62%
    - Post-implant recurrence rate at 1 year 4%
- Dexamethasone (Ozurdex)
  - Approved for BRVO and uveitis

Fluocinolone acetonide implant
- 93% develop cataracts by 3 years compared to 20% of non-implanted eyes
- 75% of patients require topical IOP lowering medications by 3 years
- 37% require glaucoma surgery by 3 years
- Surgery was considered successful in 85% of these cases at 1 year

Goldstein et al, Arch Ophthalmol 2007
Evaluation of an Intravitreal Fluocinolone Acetonide Implant versus Standard Systemic Therapy in Noninfectious Posterior Uveitis

- Randomized clinical trial in Europe comparing fluocinolone implant with corticosteroid + immunosuppressive therapy
- 140 patients, 2 year endpoint
- Implant had delayed recurrence
- 21% of implanted eyes needed IOP-lowering surgery and 88% required cataract extraction
- No significant difference in visual acuity

Pavesio et al, *Ophthalmol* 2010

The Multicenter Uveitis Steroid Treatment Trial: Rationale, Design, and Baseline Characteristics

- National Eye Institute funded randomized clinical trial comparing systemic corticosteroid and immunosuppressive therapy with fluocinolone acetonide implant
- 255 patients enrolled
- Primary outcome at 2 years
- Results expected in early 2011

*AJO, 2010*

Methotrexate

- Serious: hepatotoxicity, cytopenias, interstitial pneumonia
- Common: nausea, gastrointestinal upset, anorexia
- Teratogen
- Blood counts and liver function tests must be followed closely
Mycophenolate mofetil

- Side effects
  - GI (pain, nausea, vomiting, diarrhea)
  - Myalgias, fatigue
  - Leukopenia
  - Progressive multifocal leukoencephalopathy
- Check blood counts and liver function tests

Cyclosporine

- Adverse effects
  - Nephrotoxicity (should not use NSAIDS)
  - Hypertension
  - Hepatotoxicity
  - Gingival hyperplasia
- Must follow creatinine and blood pressure closely

Cyclophosphamide

- Adverse effects
  - Bone marrow suppression
  - Hemorrhagic cystitis
  - Reproductive failure
  - Alopecia
  - Infections
  - Teratogenic
  - Malignancy
- Require weekly and then monthly blood tests and urinanalysis
**Biologic Agents**

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>Type</th>
<th>Target</th>
<th>Route</th>
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<tbody>
<tr>
<td>Infliximab (Remicade)</td>
<td>Chimeric monoclonal antibody</td>
<td>Membrane-bound and soluble TNFα</td>
<td>IV</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>Humanized monoclonal antibody</td>
<td>Membrane-bound and soluble TNFα</td>
<td>SQ</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Recombinant human TNF receptor fusion protein</td>
<td>Membrane-bound TNFα</td>
<td>SQ</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Chimeric monoclonal antibody</td>
<td>CD20 on B cells</td>
<td>IV</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>Human fusion protein</td>
<td>B7 on T cells</td>
<td>IV</td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>Recombinant human protein</td>
<td>IL-1 receptor antagonist</td>
<td>SQ</td>
</tr>
</tbody>
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*Rheumatoid arthritis (RA), psoriatic arthritis (PA), plaque psoriasis (PP), Crohn’s disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), Juvenile idiopathic arthritis (JIA)*

Infliximab (Remicade)

- Chimeric human/murine anti-TNF alpha IgG1 (mab)
- FDA approval 1998 – rheumatoid arthritis
- Now approved for Crohn’s ds, ulcerative colitis, psoriasis, psoriatic arthritis, and ankylosing spondylitis
- Intravenous infusion given every 4 to 8 weeks

Infliximab: Side effects

- Infusion and hypersensitivity reactions
- Infections – sepsis, TB, fungi
- Malignancies – lymphoma
- Anemia and pancytopenia
- Demyelination
- Elevation of liver enzymes
- Occurrence of autoantibodies
- Onset of lupus like syndrome
Case example

- 36 year-old man with history of Behcet’s associated panuveitis with vasculitis
- Controlled well with infliximab for 5 years
- Complained of fever, cough and chills and new rash

Humira (Adalimumab)

- Human anti-TNF alpha IgG1 (mab)
- FDA approval 2002 – rheumatoid arthritis
- Now approved for psoriatic arthritis and ankylosing spondylitis
- Subcutaneous injection every 1-2 weeks

Sustained Steroid-Sparing Control with Conventional Immunosuppressive Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>6 months %</th>
<th>12 months %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>~40%</td>
<td>~57%</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>~41%</td>
<td>~55%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>~22%</td>
<td>~36%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>~30%</td>
<td>~61%</td>
</tr>
</tbody>
</table>

Data from Systemic Immunosuppressive Therapy Eye Disease studies *AJO and Ophthalmology*, 2009

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>Rate (n/N)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>32.1%</td>
<td>15.9% to 52.4%</td>
</tr>
<tr>
<td>6 months</td>
<td>62.1%</td>
<td>42.3% to 79.3%</td>
</tr>
<tr>
<td>12 months</td>
<td>62.5%</td>
<td>40.6% to 81.2%</td>
</tr>
</tbody>
</table>

Data from Proctor/UCSF Uveitis Service
Adjusted Relative Hazard of Mortality Attributed to Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>1.13 (0.60 to 2.14)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.89 (0.48 to 1.63)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0.83 (0.20 to 3.53)</td>
</tr>
<tr>
<td>Antimetabolite (in aggregate)</td>
<td>0.89 (0.54 to 1.48)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>0.82 (0.40 to 1.67)</td>
</tr>
<tr>
<td>T cell inhibitor (in aggregate)</td>
<td>0.78 (0.38 to 1.59)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>2.29 (0.53 to 9.83)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1.61 (0.81 to 3.22)</td>
</tr>
<tr>
<td>Alkylating agent (in aggregate)</td>
<td>1.74 (0.91 to 3.32)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>4.38 (0.96 to 19.93)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2.95 (0.40 to 21.83)</td>
</tr>
<tr>
<td>TNF inhibitor (in aggregate)</td>
<td>3.83 (1.13 to 13.01)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>0.92 (0.28 to 2.99)</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>1.02 (0.72 to 1.45)</td>
</tr>
</tbody>
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Kempen et al BMJ, 2009

Monitoring with systemic therapy

- Exam ~ every 2 months to monitor inflammation and pressure
- Systemic therapy requires laboratory monitoring every 1-2 months and other tests in some cases (bone density scans, blood pressure, urinalysis)
- Systemic steroids also require calcium supplementation

Quality of life

- No studies comparing quality of life between regional and systemic therapy
- Some patients do complain of constitutional symptoms (malaise, fatigue) with immunosuppressives
- Tolerance ≠ good quality of life
- Discontinuation rates of immunosuppressive therapy 10-20% per patient year
- Alcohol – prohibited with some medications such as methotrexate
- Immunosuppressive therapy contraindicated during pregnancy and breastfeeding

Summary

- Corticosteroids remain the mainstay of initial treatment
- Topical corticosteroids are sufficient for treating most cases of anterior uveitis
- Low doses of chronic topical corticosteroids are generally acceptable
- Consider implants or systemic steroid-sparing therapy for chronic inflammation
Summary

- Corticosteroid implants may be used successfully while sparing systemic side effects
- Local side effects are predictable
- Systemic steroid-sparing therapy effective but requires systemic monitoring
- Ultimate choice based on physician and patient preference and risk/benefit discussion