Ocular Involvement in Rheumatic Diseases

Wisconsin Rheumatology Association
Saturday, March 18, 2017

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Assistant Clinical Professor, Marquette University

Disclosures

• Consultant for:
  - Abbvie
  - Amgen
  - BMS
  - Celgene
  - Crescendo Bioscience
  - Genentech
  - Lilly
  - Pfizer
  - UCB
  - TREG
Objectives

- Identify rheumatic conditions that have ocular involvement
- Describe common rheumatic medications that have ocular side effects
- Discuss complications from ocular inflammation
- Review the current treatment approaches to inflammatory eye disease

Case Presentation

- 17 year-old high school student who presents with acute onset redness of both eyes. He first attributes the redness to pulling an “all nighter” in preparation for his AP biology exam. The use of OTC eye drops for 2 days gives no relief.
- He was seen by his PCP who did not think it was bacterial conjunctivitis so he was referred to ophthalmology.
- He was seen by ophthalmology and diagnosed with Episcleritis.
- He was referred to rheumatology for further evaluation and treatment.

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Case Presentation (continued)

- He was seen by you and had a completely normal physical exam except for 1+ bilateral ocular injection.
- Laboratory workup including CBC, ESR, CRP, HLA-B27, RF, ACPA, RPR, and ANA levels were all normal.
- What is the diagnosis?

Episcleritis

Episcleritis

- F>M; may affect all ages
- May be idiopathic or seen in RA (correlates with disease activity)
- Nodular vs. diffuse
- Ocular injection
- Some pain
- Rarely affects visual acuity
- Treatment
  - NSAIDS (oral/topical)
  - Artificial tears

Scleritis

- Vasculitis of the eye
- Anterior
  - Diffuse
  - Nodular
  - Necrotizing (scleromalacia perforans)
- Posterior
- Clinical features
  - Pain (worse at PM and with eye movement)
  - Ocular injection
  - Photophobia

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Ultrasound "T sign" in Scleritis

Treatment of Scleritis

- Always requires systemic therapy!!
- Corticosteroids (1mg/kg)
- DMARDs
  - Cytoxan, cyclosporine, MTX, Mycophenolate, azathioprine
- For resistant cases
  - Adalimumab
  - Infliximab
  - Rituximab

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Complications of Scleritis

- Glaucoma
- Cataract
- Scleromalacia
- Retinal detachment

Comparison of

Episcleritis

- Acute onset
- Mild pain/discomfort
- Localized or diffuse red eye
- Unilateral or bilateral
- No associated ocular symptoms other than watering and occasional mild photophobia, vision normal

Scleritis

- Subacute: usually gradual onset
- Severe boring eye pain often radiating to forehead, brow and jaw. Pain worse with movement of eye and at night (may wake patient)
- Localised or diffuse red eye
- Uni/bilateral (60% bilateral in anterior scleritis and 66% unilateral in posterior scleritis)
- Associated watering, photophobia and gradual decrease in vision
- Occasional associated systemic symptoms (fever, vomiting, headache)
- Scleromalacia perforans may present with minimal/no symptoms

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Case Presentation

• 21 year-old lady with a complaint of a rash and color changes of her hands and feet. She was sent to you by her primary care physician because of a weakly positive ANA and a concern for possible lupus.

• Her chief complaint is redness of the face and cold fingers and toes.

• On physical exam, she is noted to have a thin body habitus and weighs 110 lbs. (49.89 kg). Her BP is 110/63.

• Her physical exam is significant for a mild erythematous rash on the face and on the chest. There is mild Raynaud's changes of the digits but no ulceration or loss of digital pulp.

Case Presentation

• Her laboratory studies are completely normal except for an ANA of 1:640.

• She was started on Hydroxychloroquine 200 mg twice a day together with nifedipine10 mg every Monday, Wednesday, and Friday night. A follow-up visit was scheduled for 8 weeks.

• 10 days later she calls the office with a complaint of headaches and blurred vision. She wonders if it is due to any of her medications.

• What is the diagnosis?
Hydroxychloroquine Adverse Events

**Common**
- Dizziness
- Headache
- Ataxia
- Puritis
- Photosensitivity

**Serious**
- Cytopenias (RBC, PMN, Plts)
- Angioedema
- Exfoliative dermatitis
- Liver failure
- Vision changes/retinopathy

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Retina

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Ocular disease may be a side effect from medication: Hydroxychloroquine (HCQ)

- Retinopathy (Bull's eye maculopathy)
  - Chloroquine > HCQ >>> Quinacrine
  - 95% are reversible after stopping HCQ
  - Risk increases with: dose >6.5mg/kg; ↑BMI, diabetes


Ocular disease may be a side effect from medication: Hydroxychloroquine (HCQ)

- Corneal deposits
  - More common with chloroquine
  - Dose-dependent: rare with HCQ 400mg/day
  - Do not affect vision; reversible

- Recommendations
  - Baseline evaluation within one year; annual if normal

Case Presentation

• 32 year-old lady with sudden onset of pain and redness of the left eye. She was seen by her ophthalmologist and was diagnosed with OS anterior uveitis. She was treated with Pred Forte and homatropine eye drops.

• One week later, a repeat slit lamp evaluation showed a worsening of the cellular flare and abnormal IOP, so a sub-conjunctival injection of cortisone was given. All labs were negative except for an elevated ESR and a +HLA-B27.

• A follow-up visit in 48 hours showed no change in the degree of inflammation and the IOP had increased from 16 to 21.

• The patient was then referred to rheumatology for further evaluation and treatment.

Uveitis

• Uveitis: Inflammation of the choroid, ciliary body, and iris

• U.S. prevalence ~300,000 people
  • 75,000 with posterior, intermediate or panuveitis
  • 10,000 with refractory anterior uveitis

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Classification of Uveitis

- Anatomical
  - Anterior, intermediate
  - Posterior, panuveitis

- Descriptors
  - Onset, duration, course

- Diagnostic
  - Infectious
  - Non-infectious

Classifications by the International Study Group (Bloch-Michel, 1987)

Treatment

- Cycloplegics
- Mydriatics
- NSAIDs (oral, topical)
- Corticosteroids
  - Topical
  - Peri-ocular
  - Systemic
  - Implants

- Immunosuppressive agents
  - MTX
  - CyA (oral, topical)

- Biologic agents
  - Adalimumab
  - Infliximab
  - Others

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# Topical Corticosteroids for Ocular Inflammation

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Preparation, Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone acetate 1%</td>
<td>Pediakort</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Prednisolone Na phosphate 1%</td>
<td>Pediakort</td>
<td>Solution, BC</td>
</tr>
<tr>
<td>Dexamethasone Na phosphate 0.05%</td>
<td></td>
<td>Ointment</td>
</tr>
<tr>
<td>Loprednol etabonate 0.5%</td>
<td>Loprednol</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Dexamethasone 0.05%</td>
<td>DepoMed</td>
<td>Emulsion, SA</td>
</tr>
<tr>
<td>Moderate Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorometholone acetate 0.1%</td>
<td>Xerticon</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Fluorometholone alcohol 0.1%</td>
<td>Xerticon</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Fluorometholone alcohol 0.1%</td>
<td>FluorOint® (Novartis)</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Fluorometholone alcohol 0.1%</td>
<td>F.M.I.® (Allergan)</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Fluorometholone alcohol 0.1%</td>
<td>F.M.I.® S.O.P.® (Allergan)</td>
<td>Ointment</td>
</tr>
<tr>
<td>Loprednol 0.2%</td>
<td>Netisol®</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Rimexolone 1%</td>
<td>Vrem® (Aeon)</td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Prednisolone Na phosphate 0.125%</td>
<td></td>
<td>Suspension, BC</td>
</tr>
<tr>
<td>Prednisolone acetate 0.12%</td>
<td>Vrem® (Aeon)</td>
<td>Suspension, BC</td>
</tr>
</tbody>
</table>

BC = benzalkonium chloride; SA = sorbic acid.

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**Ways to deliver ocular medications**

- **Intraocular implants**
  - Increased risk of retinal detachment and intravitreal hemorrhage.
  - Invasive.

- **Intravitreal injections**
  - Increased risk of retinal detachment, hemorrhage, endophthalmitis and cataracts.
  - Rapidly diluted.
  - Repeat procedures necessary.

- **Systemic administration**
  - Limited/variable penetration.
  - Potential for systemic toxicity.

- **Topical application**
  - Limited penetration (<5%).
  - Rapid tear washout.
  - Poor patient compliance.

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Adalimumab in non-infectious uveitis

A Treatment Failure for Any Reason

Placebo (N=102)

Hazard ratio, 0.50 (95% CI, 0.36-0.70)
P < 0.001

Adalimumab (N=110)

No. with Failure/No. Remaining
Placebo
0/102 0/102 19/104 57/103 68/102 76/101 79/100 81/98 83/96 83/94 83/92 83/90 83/89 83/87 83/85 83/84 83/83 83/81 83/80 83/78 83/76 83/74 83/72 83/70 83/68 83/67 83/69 83/66 83/66 83/64 83/63 83/62 83/61 83/60 83/59 83/58 83/57 83/56 83/55 83/55 83/54 83/53 83/52 83/51 83/50 83/49 83/48 83/47 83/46 83/45 83/44 83/43 83/42 83/41 83/40 83/39 83/38 83/37 83/36 83/35 83/34 83/33 83/32 83/31 83/30 83/29 83/28 83/27 83/26 83/25 83/24 83/23 83/22 83/21 83/20 83/19 83/18 83/17 83/16 83/15 83/14 83/13 83/12 83/11 83/10 83/9 83/8 83/7 83/6 83/5 83/4 83/3 83/2 83/1 83/0

60-mg glucocorticoid burst and taper


Golimumab for refractory uveitis

- 15 pts with refractory anterior uveitis
  - 10/15 previously treated with TNFi

MTX therapy may prevent the onset of uveitis in JIA

- Clinical chart review of all consecutive patients (Jan 2002 to Feb 2011) with disease duration 1 year at first visit and had received stable management for ≥2 years with or without MTX
- 254 patients; 91.6% ANA+
- 86 (33.9%) treated with MTX, 168 (66.1%) did not receive MTX
- Frequency of uveitis: MTX 10.5% vs those not on MTX 20.2% (P=0.048)
- More flares with leflunomide (SAT0450)

Early MTX therapy may prevent the onset of uveitis in children with JIA

The potential of MTX to reduce the incidence of ocular disease should be investigated in a randomized controlled trial

Update on JIA-related uveitis

- TNFi is effective in JIA-related uveitis, but 20% of patients may be refractory
- Severe, MTX-resistant, JIA-related uveitis may be treated with ABA 10 mg/kg monthly before or after TNFi therapy

<table>
<thead>
<tr>
<th>Mean % uveitis flares 12 months before and after ABA</th>
<th>Pre-ABA n/year</th>
<th>Post-ABA n/year</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABA 1st (n=11)</td>
<td>4.1</td>
<td>1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>ABA 2nd (n=16)</td>
<td>3.5</td>
<td>1.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- ADA treatment improved cystoid macular edema and macular thickness
- TNFi decreased uveitis activity and induced remission in 83% of affected eyes; patients able to avoid oral prednisolone and D/C topical GC therapy

TNFi and ABA effective for refractory JIA-related uveitis

3. Alekseeva E, et al. ibid, #1148
Relative Clinical Response of TNF-i in Inflammatory Eye Disease

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Clinical Response*</th>
</tr>
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<tbody>
<tr>
<td>Etanercept</td>
<td>+/-</td>
</tr>
<tr>
<td>Infliximab</td>
<td>++</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>+++</td>
</tr>
<tr>
<td>Golimumab, certolizumab</td>
<td>+ (case reports)</td>
</tr>
</tbody>
</table>

*In combination with MTX; ocular inflammation is listed as an AE with etanercept. No data on golimumab or certolizumab.

J Smith et al. Arthritis Care and Research; 2001;44:252-257
PP Sifukai, Arthritis Care and Research; 2002;44:Suppl II:S1-53
Vazquez-Cobian LB, et al. ACR 2003, # SY24
Etanercept, package insert.

My treatment approach to inflammatory eye disease:

- Solu-Medrol 125mg IM x1; Prednisone taper 2-3 weeks
- Initiate high dose MTX (17.5 – 25 mg/week; ± subQ) with folic acid 1-2 mg per day. Consider AZA.
- Initiate adalimumab 80mg x1 then 40 mg subQ twice a month. Consider abatacept or tocilizumab.
- Imperative: weekly ophthalmology exams with confirmation of decreased cellular flare and normal ocular pressure.
- Once the ocular exam is normal, discontinue the biologic agent and slowly taper MTX over 1-3 months.
- Frequent life-long ophthalmology exams every 6-12 months.

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Rheumato-ophthalmology Potpourri

TNFi in refractory uveitis of Behcet's syndrome
Multicenter study of 63 patients (110 affected eyes)

- Prior to TNFi, patients had received IV Mpred (n=20), CyA (n=53), MTX (n=31) and AZA (n=30)
- TNF use: IFX 64%; ADA 36%
- Clinical improvement seen as early as 1 week; pts followed for up to 2 y
- SAE: 1 miliary TB

<table>
<thead>
<tr>
<th>Basal (N)</th>
<th>Patients/eyes</th>
<th>1 week</th>
<th>1 mo</th>
<th>6 mos</th>
<th>1 y</th>
<th>2 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyndall 42/68</td>
<td>28</td>
<td>97</td>
<td>80</td>
<td>88</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Uveitis 53/85</td>
<td>33</td>
<td>55</td>
<td>75</td>
<td>84</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Choroiditis 10/18</td>
<td>39</td>
<td>45</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Retinal vasculitis 55/85</td>
<td>25</td>
<td>59</td>
<td>90</td>
<td>97</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>CME (&gt;300μm) 17/24</td>
<td>13</td>
<td>13</td>
<td>63</td>
<td>63</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Monoclonal TNFi is effective and relatively safe in uveitis of Behcet's syndrome refractory to conventional therapy


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### Association of Low Vitamin D Levels With Noninfectious Anterior Uveitis

**Limouxi A, Gerting, MD; Sanamh Danesh, MD; Doumok Pamiglottok; Gegang N, Rapeluit; MD; Lusiso, MD; MHN**

**Table 2: Logistic Regression Results Examining the Association Between Low Vitamin D and Noninfectious Anterior Uveitis**

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>No. of Participants</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vitamin D level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D levels</td>
<td>100</td>
<td>100</td>
<td>2.12 (0.47-4.33)</td>
<td>.052</td>
<td>2.05 (1.45-3.22)</td>
</tr>
<tr>
<td>Vitamin D status</td>
<td>100</td>
<td>100</td>
<td>2.06 (1.35-3.14)</td>
<td>.001</td>
<td>2.05 (1.45-3.22)</td>
</tr>
<tr>
<td>Bcl-2 nuclear smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D levels</td>
<td>57</td>
<td>156</td>
<td>2.09 (0.47-4.33)</td>
<td>.052</td>
<td>2.05 (1.45-3.22)</td>
</tr>
<tr>
<td>Vitamin D status</td>
<td>57</td>
<td>156</td>
<td>2.06 (1.35-3.14)</td>
<td>.001</td>
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</tr>
<tr>
<td>Vitamin D levels</td>
<td>46</td>
<td>73</td>
<td>2.09 (0.47-4.33)</td>
<td>.052</td>
<td>2.05 (1.45-3.22)</td>
</tr>
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<td>46</td>
<td>73</td>
<td>2.06 (1.35-3.14)</td>
<td>.001</td>
<td>2.05 (1.45-3.22)</td>
</tr>
</tbody>
</table>

**Note:** OR = odds ratio; CI = confidence interval.

- In a group of 100 pts vs. 100 controls, the odds of developing uveitis were 4% lower for every 1-ng/mL increase in vitamin D level.

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**Uveitis associated with Zika virus infection:**

Slit-Lamp Photographs of the Patient's Eyes

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**Sjögren's syndrome**

- Keratoconjunctivitis Sicca
- IgG4+ disease
  - Formerly Mikulicz syndrome
  - multiorgan lymphoproliferative syndrome
- Ocular symptoms of inadequate tear production
- Ocular signs of corneal damage due to inadequate tearing
- Oral symptoms of decreased saliva production
- Salivary gland histopathology demonstrating foci of lymphocytes and IgG4+ plasma cells
- Tests indicating impaired salivary gland function
- Presence of autoantibodies (anti-Ro/SSA and/or anti-La/SSB)

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**Sjögren's syndrome**

- Treatment
  - Wetting agents
  - Punctal occlusion
  - Topical cyclosporine
  - Pilocarpine
  - Cevimeline
  - Lifitegrast
  - Interferon alpha
    - (3 MIU/d, 3x/wk for 4-8wks)


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Topical NSAIDs for Ocular Use in the United States

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Names</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurbiprofen</td>
<td>Ocuflon® (Allergan)</td>
<td>Inhibition of intraoperative miosis</td>
</tr>
<tr>
<td>Suprofen*</td>
<td>Profenal® (Alcon)</td>
<td>Inhibition of intraoperative miosis</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Acular®, Acular LS®, Acuvail® (Allergan)</td>
<td>Seasonal allergic conjunctivitis, inflammation post cataract surgery</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren® (Novartis)</td>
<td>Inflammation post-cataract surgery, photophobia/pain post refractive surgery</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>Nevanac® (Alcon)</td>
<td>Inflammation and pain post cataract surgery</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Xibrom®, Bromday™ (ISTA)</td>
<td>Inflammation and pain post cataract surgery</td>
</tr>
</tbody>
</table>


Conclusions

- Animal models suggest a role for one or more cytokines in the pathogenesis of uveitis.
- Inhibition of cytokines, especially TNF, has afforded some patients a better clinical outcome.
- Such agents may be considered in patients who are recalcitrant to local and/or systemic therapies and/or who have had complications from such therapies.
- Clinical research is on-going and these patients will be most likely treated by rheumatologists.

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Suggested Reading


