Advances in the Management of Noninfectious Uveitis

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Objectives

• To discuss advances in the systemic management of noninfectious uveitis
• To describe emerging local therapies and drug delivery for noninfectious uveitis
• To describe recent clinical trials relevant to our ability to treat patients with noninfectious uveitis
Financial Disclosures

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• Marcus Foundation/ Emory Global Health Institute (Grant)
History of Present Illness

• 62-year-old Japanese female patient
• h/o multiple prednisolone acetate tapers
• Noted to have retinal lesions and referred to retina provider
History of Present Illness

- Found to have vitritis by Retina provider
- Diagnostic pars plana vitrectomy negative for malignant cells
- Treated with oral prednisone with initial improvement but worsening with steroid taper
History of Present Illness

- Found to have vitritis by Retina provider
- Diagnostic pars plana vitrectomy negative for malignant cells
- Treated with oral prednisone (1 mg/kg) with initial improvement but worsening with steroid taper x 2
Investigations

- Labs
  - ACE 70
  - RPR, MHA-TP, PPD negative
  - HTLV I/II negative
- CXR – No evidence of sarcoidosis
- High-resolution CT
  - Mediastinal adenopathy in pretracheal regions, aorticopulmonary window, and left hilar adenopathy
Background

Uveitis is 5th leading cause of vision loss in developed countries\(^1\)

- Macular edema (ME) is the leading cause of vision impairment and vision loss in uveitis\(^2\)
- ME is common
  - 40% to 60% of intermediate, pan-, and posterior uveitis\(^3\)
  - 20% anterior\(^3\)

Therapeutic options for ME

- Local pericocular and intravitreal corticosteroids
- Systemic corticosteroids and steroid-sparing medications

2. Dick AD; Br J Ophthalmol. 1994;78:1
3. Lardenoye CWTA et al. Ophthalmology. 2006;113(8):1446
DNA → RNA → Cytokines, proteins (IL-1, IL-2, TNF-α) → Purines

Purines

Azathioprine, Mycophenolate, Methotrexate

Pyrimidines

Cyclophosphamide, Chlorambucil

Cyclosporine, FK506

Cytokines, proteins (IL-1, IL-2, TNF-α)

Infliximab (TNF-α), Adalimumab (TNF-α), Tocilizumab (IL-6)
## Systemic Immunosuppressive Therapy for Eye Diseases (SITE)

<table>
<thead>
<tr>
<th>IMT</th>
<th>No. of patients</th>
<th>Diseases</th>
<th>Inflammation control, 6 mo</th>
<th>Inflammation control, 12 mo</th>
<th>D/C Rate at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>384</td>
<td>Uveitis, Scleritis, MMP</td>
<td>20%-46%</td>
<td>66%</td>
<td>42%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>145</td>
<td>Uveitis, IU**, Scleritis, MMP</td>
<td>--</td>
<td>62%</td>
<td>~25%</td>
</tr>
<tr>
<td>MMF</td>
<td>236</td>
<td>Uveitis, Scleritis, MMP</td>
<td>53%</td>
<td>73%</td>
<td>12%</td>
</tr>
<tr>
<td>CYT</td>
<td>215</td>
<td>Uveitis, scleritis, MMP</td>
<td>49%</td>
<td>76%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Multicenter Uveitis Steroid Treatment Trial

- Prospective, randomized multicenter trial comparing standard-of-care immunosuppression to fluocinolone acetonide implant
- 255 patients randomized from 23 centers (3 countries)
- 24-month follow-up for primary safety and efficacy
- 7-year data recently published

Ganciclovir

Fluocinolone
Multicenter Uveitis Steroid Treatment Trial

- +6.0 letter improvement in implant group; +3.2 letter improvement in systemic medication group ($p=0.16$)
- Higher risk of cataract surgery (80%) and glaucoma surgery (17%) in implant group
- Higher rate of infections requiring antibiotics (0.60 vs. 0.36 patient-year, $p=0.034$)
What is a “Biologic”?  

“Wide range of products…vaccines, blood, and blood components.. gene therapy, tissues, and recombinant therapeutic proteins..  

*Biologics* are isolated from a variety of natural sources – human, animal or microorganism – and may be produced by biotechnology methods”

www.fda.gov

<table>
<thead>
<tr>
<th></th>
<th>Biologics</th>
<th>Conventional Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing process</td>
<td>Manufactured in a living system</td>
<td>Chemical synthesis</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>Complex, sometimes difficult to characterize</td>
<td>Well-defined structure</td>
</tr>
</tbody>
</table>
Biologic Therapies

**Anti-TNF**
- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Etanercept (Enbrel)

**Anti-IL-6**
- Tocilizumab (Actemra)

**CTLA4-IgG1 fusion protein (Co-stimulation inhibitor)**
- Abatacept (Orencia)

Adalimumab (Humira) for active uveitis

Multinational phase 3 trial for **active** intermediate, posterior or panuveitis

- 1:1 Randomization
  - Adalimumab (80 mg loading, 40 mg q 2 weeks) vs. placebo
- Patients received oral prednisone burst, followed by tapering over 15 weeks
- **Primary Efficacy Endpoint:** Time to treatment failure after 6 weeks
- Treatment Failure: Multi-component outcome based on new inflammatory lesions, BCVA, AC cell, and vitreous haze

Jaffe et al *NEJM* 2016
Adalimumab (Humira) for active uveitis

Treatment failure for any reason

Time to treatment failure was 24 weeks in the adalimumab group vs. 13 weeks in the placebo group.

Adalimumab group less likely than placebo to have treatment failure (Hazard ratio 0.50, 95% CI 0.36 to 0.70, P< 0.001)

Jaffe et al NEJM 2016
Adalimumab (Humira) for inactive uveitis

Multinational phase 3 trial for inactive intermediate, posterior or panuveitis in patients on prednisone 10 – 35 mg/day

• 1:1 Randomization
  – Adalimumab (80 mg loading, 40 mg q 2 weeks) vs. placebo

• Mandatory prednisone taper at week 2

• Primary Efficacy Endpoint: Time to treatment failure

• Treatment Failure: Multi-component outcome based on new inflammatory lesions, BCVA, AC cell, and vitreous haze

Nguyen et al Lancet 2016
Adalimumab (Humira) for inactive uveitis

Treatment failure for any reason

Time to treatment failure was 18 months in the adalimumab group vs. 8.3 months in the placebo group

Hazard ratio 0.57, 95% CI 0.39-0.84, P=0.004

Nguyen et al Lancet 2016
**Interleukin-6 inhibition**

**Pleitropic cytokine** implicated in many immune-mediated disorders including uveitis. Uveitis syndromes where IL-6 implicated include Behcet’s disease, VKH and sarcoidosis.

**Cellular basis:** Differentiation of T-cells into TH1 and TH17 cells.

**Signaling basis:** IL-6/IL-6R binding → gp130 signal transduction → JAK/STAT pathways → IL-6 responsive genes (CRP, fibrinogen, VEGF)
Tocilizumab (Actemra) for refractory uveitis

Birdshot retinochoroidopathy (Calvo Rio et al)
- Two patients who had failed multiple agents (corticosteroid, TNF-alpha inhibition)
- Visual acuity and OCT improved in all four eyes
- Corticosteroid-sparing effect also observed

Uveitic macular edema (Deuter et al)
- Eight eyes of 5 patients treated previously with corticosteroid, at least one immunosuppressive drug, and a biologic
- At 3 months, $\geq 25\%$ reduction in macular edema achieved in 6 eyes (75%)
- Complete resolution of macular edema in 5 of eight eyes (62.5%)
- Tocilizumab was well-tolerated with no side effects

Calvo-Rio et al *Ocular Immunol and Inflammation*
Deuter et al *Ocular Immunol and Inflammation*
Long-term effects of tocilizumab for macular edema due to uveitis

- Eleven eyes of 7 patients
- Mean duration of ME was > 14.2 years; Mean F/U 15.2 months
- Diagnoses: Birdshot (3), JIA (3), Idiopathic panuveitis (1)
- Mean central foveal thickness improved from 550 um to 274 um at 12-months (P=0.002)
- Mean logMAR BCVA improved from 0.67 to 0.4 at 12-months (P=0.008)

Mesquida et al *Ophthalmol* 2014
Long-term effects of tocilizumab for macular edema due to uveitis

Mesquida et al. Ophthalmol 2014

Baseline

12 months

Medication withdrawal

Medication restarted
Rituximab for refractory scleritis and uveitis

Prospective, dose-ranging, randomized, double-masked Phase I/II clinical trial

Patients randomized to 500 mg (n=5) or 1000 mg (n=7) arms of rituximab at study day 1 and day 15

Primary outcome

1. Reduction of inflammation by scleritis grading scale
2. Reduction of corticosteroid by ≥ 50%

Nine patients met SGS endpoint; 4 patients reduced corticosteroid by ≥ 50%

Suhler et al Ophthalmology 2014
Rituximab for refractory scleritis and uveitis

- 64 year-old female patient with rheumatoid arthritis & chronic inflammatory demyelinating polyneuropathy
- Bilateral, diffuse anterior and posterior scleritis with panuveitis
- Refractory/recurrent disease despite methotrexate, cyclophosphamide, adalimumab, oral prednisone
Rituximab for refractory scleritis and uveitis

20/400
s/p Rituximab and IV solumedrol
Local Corticosteroid and Immunotherapeutic Options

- **Dexamethasone**
  - 0.7 mg (Ozurdex)
  - Intravitreal injection
  - 22-gauge
  - Duration: 4-6 months
  - HURON Trial

- **Fluocinolone acetonide**
  - 0.59 mg (Retisert)
  - Surgical intravitreal implant
  - 3.5 mm wound
  - Duration: 30 months
  - Multicenter Uveitis Steroid Treatment (MUST) Trial

- **Triamcinolone acetonide**
  - 4 mg (Triescence; Kenalog)
  - Intravitreal; Periocular
  - 25- or 27-gauge
  - Duration: 4-6 months
  - **POINT Trial Ongoing**
    - Sen et al. Ophthalmology 2014
    - Leder, Thorne et al. AJO 2011

- **Fluocinolone acetonide implant**
  - (SAKURA)

- **Sirolimus (mTOR Inhibition)**
  - Ibrahim, Nguyen et al. TVST 2015
  - (SAVE)

- **Suprachoroidal triamcinolone acetonide**
  - Goldstein et al. TVST 2016

**Novel Local Therapies**
Suprachoroidal Injection for Posterior Segment Disease

• **Novel technique for suprachoroidal injection**
  – 30G needle approx. 1000 micron in length
  – Proprietary microinjector syringe

• **Potential benefits**
  – Efficacy advantages due to higher bioavailability
  – Longer duration
  – Fewer side effects
Suprachoroidal Drug Delivery: Laboratory Investigation

Chorioretinal Selectivity =
Concentration of NaF at choroid/retina interface versus lens/vitreous

Pharm Research 2011

Patel S. et al IOVS 2012

10-fold greater chorioretinal selectivity with suprachoroidal over IVT
Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Phase I/II Study

Study Design

- Single suprachoroidal injection of triamcinolone acetonide (TA) 4 mg/0.1 mL following topical anesthetic
- Safety, tolerability, and preliminary efficacy evaluated
- 26-week follow-up

Participants (Anatomic Classification)

- Anterior/Intermediate (3, 33%)
- Intermediate (1, 11%)
- Panuveitis (5, 56%)
Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Safety and Tolerability

Table 2. Ocular Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence, N = 11, n (%)</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye pain</td>
<td>5 (45)</td>
<td>6</td>
</tr>
<tr>
<td>Cystoid ME&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (27)</td>
<td>4</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>2 (18)</td>
<td>2</td>
</tr>
<tr>
<td>Vision blurred&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (9)</td>
<td>2</td>
</tr>
<tr>
<td>Cataract&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Cataract operation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Eyelid margin crusting</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Retinal ischemia</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Retinal neovascularization</td>
<td>1 (9)</td>
<td>1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1 (9)</td>
<td>1</td>
</tr>
</tbody>
</table>

Goldstein et al; TVST Dec 2016
Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Efficacy

Central retinal thickness reduction
- Mean reduction in CRT 154 um by week 8
- 20% reduction in baseline CRT in 4/7 patients

Visual acuity improvement
- Mean logMAR VA improvement ranged from 0.17 to 0.28 (i.e. 8 to 14 letters)

Goldstein et al; TVST Dec 2016
The study was a randomized, masked, controlled, multi-center study in subjects with uveitis.

- Macular edema ≥310 µm in the central subfield (CSF) using a Heidelberg Spectralis.
- ETDRS BCVA score of ≥ 20 letters read (20/400 Snellen approximate) in each eye.
- Study was powered only for the 4.0 mg dose; only these data will be presented.
## Diagnosis Overview / Uveitis Distribution

<table>
<thead>
<tr>
<th>Classification of Uveitis n (%)</th>
<th>CLS-TA 4.0 mg (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Eye</td>
<td></td>
</tr>
<tr>
<td>Anterior Uveitis</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Intermediate Uveitis</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Posterior Uveitis</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>9 (52.9)</td>
</tr>
</tbody>
</table>
## Diagnosis Overview / Uveitis Distribution

<table>
<thead>
<tr>
<th>Diagnoses Associated with Noninfectious Uveitis – N (%)</th>
<th>CLS-TA 4.0mg (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Behcet’s Syndrome</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>HLA-B27 Related</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Birdshot Retinochoroidopathy</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Pars Planitis</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
</tbody>
</table>

- **CLS**: Clasquin 4.0mg
Reduction in Central Subfield Thickness (4 mg)

Mean baseline = 526 µm
Illustrative Patient

Pre

20/80

2 mo post CLS-TA

20/32
Visual Acuity Improvement: 4.0 mg Dose

BCVA letters read change from baseline

Month 1: 7.7
Month 2: 9.2

p = 0.0001
p = 0.0004

Mean baseline = 60 letters

N=17
ITT population
# Ocular Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CLS-TA 4.0 mg N=17; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of adverse events</strong></td>
<td><strong>12</strong></td>
</tr>
<tr>
<td>Number of subjects with at least 1 AE</td>
<td><strong>8 (47)</strong></td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td><strong>6 (35)</strong></td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Dry Eye</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Eye Pain</td>
<td><strong>3 (18)</strong></td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Uveitis</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td><strong>General disorders and admin. Site Conditions</strong></td>
<td><strong>2 (12)</strong></td>
</tr>
<tr>
<td>Injection site pain</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Papillitis</td>
<td><strong>1 (6)</strong></td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td><strong>1 (6)</strong></td>
</tr>
</tbody>
</table>
Intraocular pressure - 4.0 mg Dose

N=17
Safety population

22 mmHg

IOP [mm Hg]

Pre-Dose (Day 1)*  Post-Dose (Day 1)*  Week 2  Month 1  Month 2

* Within 30 min of injection

Max Outlier

Intraocular Pressure Safety Set Listing 16.2.6-1.3 (1/18/16)
Intravitreal Sirolimus: A Novel Immunoregulatory Agent

- Locally delivered mTOR inhibitor for non-infectious uveitis of the posterior segment (NIU-PS)
- Immunoregulates by interrupting the inflammatory cascade and promoting immune tolerance\(^1,2\)
  - Inhibits T-cell activation, proliferation, and differentiation
  - Increases regulatory T lymphocytes (Tregs)
- Proprietary IVT formulation\(^3\)
  - Forms depot in vitreous
  - Slow diffusion over 2 months
  - Minimal systemic exposure

Images courtesy of Q. Nguyen.
IL, interleukin; IVT, intravitreal; mTOR, mammalian target of rapamycin.
SAKURA Study 1 Design: 3 Active Arms

Patients initially continued on their assigned group. Subsequent study amendments called for all patients to receive 880 µg starting at Month 6. Subjects must meet retreatment criteria to receive injections. Denotes subjects who received treatment during this period.

Study report date 10/2015.

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Intravitreal sirolimus:
- 44 µg (Active Control)
- 440 µg
- 880 µg
- 880 µg PRN

### Primary Endpoint
- Double-Masked (Active Control) N = 347
- Open-Label (880 µg) n = 211c

### Monthly Dosing
- Month 0-4: 44 µg
- Month 5: 440 µg
- Month 6: 880 µg PRN

Open-Label PRN Dosing n = 132c

Final Visit
SAKURA Key Inclusion/Exclusion Criteria

- Age ≥18 years
- Diagnosis of active NIU of the posterior segment (investigator determined)
  - If an anterior component is present, it must be less than the posterior component
- VH score >1+ (study eye) (modified SUN scale)
- BCVA: ≥19 ETDRS letters or 20/400 (study eye)
- Vision ≥20/200 (fellow eye)
- Uncontrolled glaucoma (IOP >21 mm Hg while on medical therapy)
- Active infectious uveitis
- Ocular or periocular infection
- Vision-compromising ocular diseases (including, but not limited to, PDR, NPDR, neovascular AMD, CVO)
- Lens opacities that prevent reliable posterior segment evaluation
- Previous vitrectomy
- Recent intraocular surgery

ETDRS, Early Treatment Diabetic Retinopathy Study; VH, vitreous haze; BCVA, best corrected visual acuity; IOP, intraocular pressure; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; AMD, age-related macular degeneration; CVO, central vein occlusion.
SAKURA: Primary Endpoint

- VH = 0 response rate at Month 5 (study eye)$^a$

- SAKURA used a modified SUN Scale that included a VH of 1.5+$^b$

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$^a$Intent-to-treat population with last observation carried forward (LOCF). Subjects rescued before Month 5 are treated as non-responders.

$^b$Defined as optic nerve head and posterior retina view obstruction >1+ but <2+.
SAKURA: Key Secondary Endpoints

• VH = 0 or 0.5+ response rate at Month 5 (study eye)\textsuperscript{a}
• VH = 0 or ≥2-unit improvement response rate at Month 5 (study eye)\textsuperscript{a}
• Corticosteroid tapering success rate: the overall prednisone-equivalent dose tapered to ≤5 mg/d at Month 5\textsuperscript{b}

\textsuperscript{a}Intent-to-treat population with last observation carried forward. Subjects rescued before Month 5 are treated as non-responders.
\textsuperscript{b}For the intent-to-taper population; ie, subjects who were taking systemic corticosteroid(s) at Day 1 (Baseline) with the overall prednisone-equivalent dose >5 mg/d.
Primary Endpoint: Proportion of Subjects With \( VH = 0 \) at Month 5\(^a\)

Results are for the study eye.

Adjusted for multiplicity. \( p \)-value is for comparison between the 440-\( \mu \)g dose and the 44-\( \mu \)g (active control) dose of intravitreal sirolimus.

\(^a\)Results are for the study eye.

\(^b\)Adjusted for multiplicity. \( p \)-value is for comparison between the 440-\( \mu \)g dose and the 44-\( \mu \)g (active control) dose of intravitreal sirolimus.
Tapering Successes: Proportion of Subjects With the Overall Prednisone-Equivalent Dose Tapered to ≤5 mg/d at Month 5 (Intent-to-Taper Population)

Subjects randomized through March 31, 2013. Study report date October 2015.
Intraocular Pressure: Raw Mean (SE) Change From Baseline by Analysis Visit

Results are for the study eye.

Raw Mean (SE) Change From Baseline in Intraocular Pressure (mm Hg)

- 44/880 µg (Active Control)
- 440/880 µg
- 880/880 µg

Denotes Open-Label Dosing With 880 µg

aResults are for the study eye.
Fluocinolone acetonide injectable (FAi)

• Jaffe et al treated 11 eyes of 11 patients
• VA improved from 0.56 logMAR to 0.25 logMAR and 0.17 logMAR VA at 12 and 24 months
• Average # of recurrences in 12-months pre-implant = 1.54 → No recurrences post implant

Jaffe et al *Ophthalmol* 2016
Summary

• Improved understanding of conventional immunosuppressive medication, side effect profiles, and efficacy
• Increasing numbers of biologics (e.g. monoclonal antibodies, soluble protein receptors) used in the treatment of uveitis
• Local therapeutics involve changes in drug delivery strategy (suprachoroidal) and different mechanism of action compared to corticosteroids (mTOR inhibition)