Front-line Local Therapies for Uveitis:  
From Clinical Trials to Practice

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Angiogenesis, Exudation and Degeneration 2020  
17th Annual Meeting  
Miami, Florida  
February 8th, 2020
Financial Disclosures

Clearside Biomedical (Consultant, Grant)
Santen (Consultant, Advisory Board, Grant)
National Institutes of Health (Grant)
Research to Prevent Blindness (Grant)
Bayer Global Ophthalmology Awards Program (Grant)
Overview

• Multicenter Uveitis Steroid Treatment Trial (MUST Trial - Fluocinolone acetonide vs. Systemic Immunosuppression)
• POINT Study – Ozurdex vs. Triamcinolone vs. Periocular Corticosteroid
• Fluocinolone acetonide insert (Yutiq)
• Suprachoroidal drug delivery (Xipere)
• Anti-VEGF therapy
Macular edema is the **leading cause of vision impairment in uveitis**

**Therapeutic options for ME**

- Local corticosteroid injections and topical eye drops
- Systemic immunosuppression
- Other local therapies
  - Anti-VEGF
  - Methotrexate
  - Sirolimus

2. Dick AD; Br J Ophthalmol. 1994;78:1
3. Lardenoye CWTA et al. Ophthalmology. 2006;113(8):1446
Multicenter Uveitis Steroid Treatment (MUST) Study

- Comparative efficacy trial assessing efficacy and safety of standard-of-care systemic immunosuppression vs. FA implant (Retisert)
- 0.59 mg implant, requiring surgery
- Risk of drug core dislocation, single-piece device now available

Photo Credit Dr. Thomas Albini
Multicenter Uveitis Steroid Treatment (MUST) Study

- Corticosteroids plus systemic IMT vs. fluocinolone acetonide implant for NIU

  - Efficacy
    - Visual acuity improvements comparable between systemic and FA implant
    - Residual active inflammation favored implant vs. systemic IMT (12% to 29%)

  - Safety
    - Higher rates of cataract (80%) and glaucoma (17%) in implant group
    - Higher rate of prescription-requiring infections in systemic IMT group

Percentage with active uveitis

<table>
<thead>
<tr>
<th>Months</th>
<th>Systemic IMT</th>
<th>FA Implant</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td></td>
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<td>12</td>
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<tr>
<td>18</td>
<td></td>
<td></td>
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<tr>
<td>24</td>
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*Calculated from the subset of eyes with uveitis at enrollment
† At enrollment, the difference in the proportion with activity was 2% (p = 0.0197)
‡ The bootstrap was used to estimate 95% confidence intervals at enrolment, 6 months, 1 year, and 2 years
Triamcinolone = Ozurdex > Periocular for Both Metrics

Fluocinolone Acetonide Intravitreal Microinsert 0.18 (FAi), 36-month drug delivery

- Rod-shaped, non-bioerodible device
- 25-gauge injector
- Two multicenter RCTs, randomized 2:1, FAi vs. Sham
  - PSV-FAi-001 – Multinational trial
  - PSV-FAi-005 - Multisites (India)
  - Primary endpoint: % patients requiring rescue within 6 months
Fluocinolone Acetonide Intravitreal Insert for Macular Edema due to Noninfectious Uveitis

- Reduced rate of vision loss
- Reduced need for adjunctive treatment in FAi

Jaffe et al, Ophthalmology 2019

Cataract requiring surgery: 33% in FAi; 5% in sham
IOP-lowering medications: 26% in FAi and in sham
Suprachoroidal Injection with the SCS Microinjector™
PEACHTREE: Phase 3, Randomized, Controlled, Double-Masked, Multicenter Trial

Primary endpoint: Visual Acuity

Active Arm: Suprachoroidal injection of 4 mg CLS-TA

Control Arm: Sham injection procedure

Enrollment

N=96
Day 0 Wk 4 Wk 8 Wk 12 Wk 16 Wk 20 Wk 24
Suprachoroidal CLS-TA

N=64
Day 0 Wk 4 Wk 8 Wk 12 Wk 16 Wk 20 Wk 24
Sham

Both Arms: Rescue therapy at any time according to pre-specified criteria

Evaluation period – 6 months

PEACHTREE Study Investigators, Ophthalmol 2020
PEACHTREE Met Its Primary Efficacy Endpoint

Subjects gaining > 15 ETDRS letters, %

\[ p < 0.001 \text{ for comparison} \]

Intention-to-treat population; LOCF imputation.

The p-value is based on a CMH Cochran-Mantel-Haenszel test for general association between treatment and response with stratification by country.

ETDRS, Early treatment diabetic retinopathy study; LOCF, last observation carried forward.
MAGNOLIA: Prospective, Non-interventional, Masked, Observational 24-week Extension Trial

- To be eligible for MAGNOLIA, subjects must have completed PEACHTREE and NOT have received rescue medication.
- Primary Endpoint: Time to rescue therapy relative to Day 0 of PEACHTREE.

Rescue criteria:
- Loss of 10 letters from either of prior 2 visits
- CST > 320 μm
- ↑ CST of 100 μm or 20% (whichever is lower) from either of prior 2 visits
- Investigator discretion
Primary Endpoint:
Kaplan-Meier Plot Time to First Rescue

- 50% of CLS-TA subjects did not receive any additional medication through Week 48
- 9 months from last CLS-TA dose

No significant differences in baseline characteristics were seen between patients who enrolled in MAGNOLIA vs patients who were eligible to enroll in MAGNOLIA but didn’t.
Anti-VEGF for macular edema due to NIU

Ranibizumab (RZB) for ME
Acharya et al AJO 2009

- Monthly injections of RZB for ME due to NIU x 3 months
- 13-letter VA gain with OCT improvement
- Seven patients enrolled

Ranibizumab (RZB) for ME
Reddy et al Retina 2014

- OCT-guided RZB injections for ME due to NIU
- ~12-letter gain over time with OCT improvements over 12 months
Anti-VEGF for macular edema due to NIU

Phase 3 RCT, sham controlled study, 178 pts randomized to 0.5 mg ranibizumab (n=110) 0.5 mg or sham (n=68) at month 0 and 1

- Open label at 2-months thereafter according to disease activity
- +5.8 letters (treatment), +2.9 in sham (p=0.011)

Staurenghi et al Ophthalmology 2018
Phase 3 RCT, sham controlled study, 178 pts randomized to 0.5 mg ranibizumab (n=110) 0.5 mg or sham (n=68) at month 0 and 1

- Open label at 2-months thereafter according to disease activity
- +5.8 letters (treatment), +2.9 in sham (p=0.011)
- 21 patients randomized from the uveitis cohort

**PROMETHEUS Study**
Ranibizumab for ME due to ‘uncommon causes’

<table>
<thead>
<tr>
<th>Baseline ME etiology</th>
<th>n (%)</th>
<th>Ranibizumab</th>
<th>Sham</th>
<th>Favor sham (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>177 (100)</td>
<td>5.7</td>
<td>2.9</td>
<td>2.78 (0.40, 5.16)</td>
</tr>
<tr>
<td>Inflammatory/post-uveitis</td>
<td>21 (11.9)</td>
<td>0.2</td>
<td>0.8</td>
<td>5.45 (~2.38, 13.29)</td>
</tr>
<tr>
<td>Pseudophakic/aphatic</td>
<td>58 (32.8)</td>
<td>9.1</td>
<td>3.2</td>
<td>5.86 (0.91, 10.81)</td>
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<tr>
<td>CSC</td>
<td>26 (14.1)</td>
<td>3.0</td>
<td>2.5</td>
<td>0.54 (~3.70, 4.79)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>51 (28.8)</td>
<td>3.0</td>
<td>4.4</td>
<td>-6.49 (~6.10, 5.11)</td>
</tr>
<tr>
<td>Miscellaneous**</td>
<td>22 (12.4)</td>
<td>4.3</td>
<td>1.1</td>
<td>3.29 (~1.97, 5.49)</td>
</tr>
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Staurenghi et al Ophthalmology 2018
Summary

• Phase 3 studies have demonstrated the benefit of local corticosteroids via novel drug delivery platforms for macular edema due to noninfectious uveitis

• Other agents (ranibizumab, methotrexate, and sirolimus) remain under investigation for noninfectious uveitis

• Promising outlook for local delivery options for noninfectious uveitis