Advances in Treating Macular Degeneration

Geeta Lalwani, MD
Rocky Mountain Retina Associates
303-963-9669

Bascom Palmer Eye Institute
#1 Eye Institute 12 years in a row!

- Clinical professor of ophthalmology-vitreoretinal surgery
- Areas of Research
  - Age related macular degeneration
  - Diabetes
    - Surgical Management
    - Diabetic Macular Edema
  - Spectral Domain OCT

Training

- Smith College- Massachusetts
  - Chemistry & Japanese
- MCP-Hahnemann- Philadelphia, PA
- Case Western Reserve- Cleveland, OH
- Bascom Palmer Eye Institute, Miami, FL
  - 2 year surgical fellowship in retina

Disclosures

- Consulting Fees: Allergan, Alcon, B&L, Genentech, Novartis, Regeneron, DORC
- Ownership interests: Ocugen
Outline

• Definitions
• Tools to assess and monitor intermediate to late disease
• Minimizing progression
• Current and emerging options for treatment
• Improving patient quality of life through vision loss aids and services

Early & Intermediate AMD

• Early AMD
  – Fine drusen, RPE mottling
• Intermediate AMD
  – Small, intermediate, or large sized drusen
  – Chorioretinal atrophy
  – RPE hyperplasia (“pigment”)
**AMD Spectrum**

- **Intermediate**
  - High-risk Dry AMD

- **Advanced Dry AMD:**
  - Geographic Atrophy
  - Hypopigmentation
  - Hyperpigmentation

**Development of Atrophy**

- **DRUSEN**
  - Large Confluent Drusen
  - Hyperpigmentation
  - Hypopigmentation

- **ANGIOGENESIS**
  - CNV
  - Fluid
  - Hemorrhage
  - Fibrosis
  - PED
  - RPE Tear

- **FOCAL CHORIORETINAL & RPE ATROPHY**

- **GEOGRAPHIC ATROPHY**

**Example of GA Progression**

- 1993: Baseline
- 1999: Onset of GA

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**Metamorphopsia & Scotoma**

Normal

Abnormal

**Digisight: Paxos Checkup**

**Home Monitoring for CNV**

Foresee Home monitoring System
- High risk dry AMD in both eyes
- Vision better than 20/60

**HOME Study Background**

Randomized 1:1 to AMD monitoring device + standard care (device monitoring arm), or standard care alone to determine which arm improved the detection of the progression to CNV in dry AMD eyes

Part of the National Eye Institute’s (NEI) Age-related Eye Disease Study 2 (AREDS2) on nutritional supplements in the prevention of AMD.

1,520 participants

44 Centers
Defining CNV Events

Changes in vision were detected by the AMD monitoring device using Preferential Hyperacuity Perimetry (PHP), causing an “alert” when significant changes were detected by the device, by symptoms or during office visits.

Standard Care Arm: 31 CNV Events

Changes in vision were detected by symptom realization by the participant or during office visits.

Device Monitoring Arm: 51 CNV Events

# of Letters of Lost

<table>
<thead>
<tr>
<th></th>
<th>Standard care Cohort</th>
<th>FSH ITT Cohort</th>
<th>FSH PP1 Cohort</th>
<th>FSH PP2 Cohort</th>
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<tr>
<td>n</td>
<td>30</td>
<td>51</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Mean</td>
<td>-4.0</td>
<td>-3.0</td>
<td>-3.0</td>
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<tr>
<td>P</td>
<td>.007</td>
<td></td>
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<td>.003</td>
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</table>

P = .021

* Excluded one eye with no VA data at the time of CNV Event

Proportion of Patients 20/40 or Better

<table>
<thead>
<tr>
<th></th>
<th>Standard Care</th>
<th>FSH ITT Cohort</th>
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<th>FSH PP2 Cohort</th>
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<tbody>
<tr>
<td>% of Eyes Maintaining Functional Vision of 20/40</td>
<td>62%</td>
<td>87%</td>
<td>91%</td>
<td>94%</td>
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<tr>
<td>n</td>
<td>18</td>
<td>40</td>
<td>32</td>
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P = .014

P = .005

P = .003

Early Efficacy = Early End to the Study

- The Data Safety and Monitoring committee recommended study termination at the interim analysis of 80% of the target CNV events for the HOME Study, because the study demonstrated that eyes that progressed to neovascular AMD, were identified with significantly better levels of visual acuity in the device monitoring arm compared to standard care alone.
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Aging and Malnutrition

- Of those over age 65 in community setting:
  - 5% to 10% are malnourished
  - 35% in long-term care facilities
  - 60% in hospitals

Eating a Healthy Balanced Diet

Avoidance of Smoking

Rate to Advanced AMD
AMD Categories 3 and 4 by Treatment Group

Estimated Probability

- Placebo
- Antioxidants
- Zinc
- Antioxidants + Zinc

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Antioxidants</th>
<th>Zinc</th>
<th>Antioxidants + Zinc</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>30%</td>
<td>28%</td>
<td>20%</td>
<td>10%</td>
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</tbody>
</table>

*Estimated Probability*

- Placebo
- Antioxidants
- Zinc
- Antioxidants + Zinc

$P$ vs. A+Z – $P < .01$

$P$ vs. Z – $P < .01$

AREDS SIMPLIFIED SYSTEM
SCORE OF 0 TO 4 POINTS

**Right Eye**
- Large Drusen
  - No = 0
  - Yes = 1
- Pigment Changes
  - No = 0
  - Yes = 1

**Left Eye**
- Large Drusen
  - No = 0
  - Yes = 1
- Pigment Changes
  - No = 0
  - Yes = 1

Large Drusen and Pigment Changes

Patient Severity Score
- 4 Risk Factors

Risk of Progression to Advanced AMD

<table>
<thead>
<tr>
<th>Score</th>
<th>Estimated Probability</th>
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<tbody>
<tr>
<td>0</td>
<td>43% 5-year risk</td>
</tr>
<tr>
<td>1</td>
<td>27% 5-year risk</td>
</tr>
<tr>
<td>2</td>
<td>9% 5-year risk</td>
</tr>
<tr>
<td>3</td>
<td>3% 5-year risk</td>
</tr>
<tr>
<td>4</td>
<td>1% 5-year risk</td>
</tr>
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Micronutrient Supplementation

AREDS and AREDS2

Age-Related Eye Disease Study

Age-Related Eye Disease Study 2
**Age Related Eye Disease Study**

**AREDS I**
- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Zinc (80 mg)
- Copper (2mg)
- Beta carotene (15 mg)

**AREDS II**
- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Zinc (80 mg)
- Copper (2mg)
- Lutein (10mg)
- Zeaxanthin (2mg)
- ? Omega 3

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**AREDS2: Beta-Carotene?**

- There was no apparent effect of beta-carotene elimination or lower-dose zinc on progression to advanced AMD.
- More lung cancers were noted in the beta-carotene vs no beta-carotene group (23 [2.0%] vs 11 [0.9%], nominal $P=.04$), mostly in former smokers.

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**AREDS 2 Bottom Line**

- Negative study
- Addition of omega-3 fatty acids not beneficial
- Use a lutein/zeaxanthin-containing preparation in place of beta-carotene OK
  - No need to have the “if you are a smoker” discussion

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**Carotenoids Age-related Eye Disease Study (CAREDS)**

- Adherence to a Mediterranean diet associated with lower prevalence of early AMD
  - Diet scored on intake of vegetables, fruit, legumes, alcohol and ratio of monounsaturated fats
  - Adjusted for demographic, behavioral, ocular and genetic factors
• High score associated with 26% reduced risk with progression to advanced AMD
  – Addition of supplements did not have an impact


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Treatments: Wet AMD

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<thead>
<tr>
<th>CURRENT &amp; PAST</th>
<th>FUTURE</th>
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</thead>
<tbody>
<tr>
<td>• Micronutrients</td>
<td>• Synergistic therapies</td>
</tr>
<tr>
<td>• Anti-VEGF Agents</td>
<td>• Longer-lasting molecules</td>
</tr>
<tr>
<td>• Photodynamic Therapy</td>
<td>• Sustained release implants</td>
</tr>
<tr>
<td>• Thermal Laser</td>
<td>• Gene therapy</td>
</tr>
</tbody>
</table>

Anti VEGF Agents

• AVASTIN
  – First anti VEGF used publically (2005)
  – Originally developed for Colon CA treatment
  – Numerous head to head trials fro AMD (and other diseases) demonstrates equal efficacy and safety

• LUCENTIS
  – First FDA approved anti VEGF (2006)
  – Strong safety data

• EYLEA
  – Combined anti VEGF and anti PDGF
  – Non-inferior to Lucentis
New anti VEGF - Brolucizumab

- Smaller molecule with better retinal penetration
- Perhaps longer duration therefore requiring fewer injections
- FDA approved- available 2019

Injections for wet AMD

- Chronic treatment
- Will start as monthly treatments and slowly increase interval between treatments
- NO PAIN with the injections

Current Treatments: Dry AMD

<table>
<thead>
<tr>
<th>Drusen</th>
<th>Geographic Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronutrients</td>
<td>None</td>
</tr>
</tbody>
</table>

Future Treatments: Dry AMD

<table>
<thead>
<tr>
<th>Drusen</th>
<th>Geographic Atrophy</th>
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</thead>
<tbody>
<tr>
<td>Micronutrients</td>
<td>Complement Inhibitors</td>
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<tr>
<td>Complement Inhibitors</td>
<td>Gene therapy</td>
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<tr>
<td>Gene therapy</td>
<td>Stem cell therapy</td>
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</table>
Complement Inhibitors in Clinical Trials

- Anti-C3 cyclic peptide
  - POT-4 (intravitreal)
  - APL-2 (intravitreal)
- Anti-C5 drugs
  - Anti-C5 aptamer (ARC1905) (intravitreal)
- Anti-C5 monoclonal antibodies:
  - LFG316 (intravitreal)
  - Eculizumab (intravenous)
- Anti-Factor D Fab
  - Lampalizumab (intravitreal)

Slide Courtesy of Philip J. Rosenfeld, MD, PhD

Current Hypothesis for GA Pathophysiology

- Oxidative stress
- Genetic predisposition
- Environment

Complement deposition between retinal pigment epithelium (RPE) and Bruch’s membrane
- Loss of complement regulation
- Blood-retina barrier breakdown

Geographic atrophy


Factor D is Required for the Activation of the Alternative Complement Pathway

Binding of Lampalizumab to Factor D Inhibits Activation of the Alternative Pathway Cascade


The Lampalizumab Clinical Trial Program
- Designed to address an unmet need for >5 million GA patients globally

4 Studies | >2400 GA Patients | >275 Sites | >20 Countries

Interventional
- Chroma
- Spectri

Observational
- Proxima A
- Proxima B

Two identically designed, randomized, Phase III, pivotal studies

Two separate, parallel, prospective, observational studies


Lampalizumab
- Failed to meet its Phase III clinical endpoint
- No longer being explored as a treatment

Visual Function Endpoints
Phase III Secondary Efficacy Endpoints Will Evaluate Visual Function Outcomes Potentially More Relevant for GA Patient’s Quality of Life

Interventional
- Chroma
- Spectri

Observational
- Proxima A
- Proxima B

Visual Function Questionnaire measures vison-targeted health status

Reading speed

PRO (VFQ-25)

Microperimetry

LLVA

BCVA

GA, low luminance visual acuity; PRO, patient reported outcome. Regillo CD, presented at Angiogenesis, Exudation, and Degeneration 2015.
Possible New Treatment for Dry AMD
C3 Inhibitor APL-2

1. Phase II study with 246 patients for 12 months
2. 29% reduction in the rate of geographic atrophy through 12 months with monthly injections
   - Increase in development of wet AMD IF patients already had wet AD in the fellow eye
3. Starting phase III in mid 2018

Possible New Treatments to Reverse Dry AMD

- Reverse the damage from GA
  - Stem Cells
  - Gene Therapy

Possible New Treatments for GA

- Subretinal Implantation of Retinal Pigment Epithelial Cells Derived From Human Embryonic Stem Cells: Improved Survival When Implanted as a Monolayer

Possible New Treatments for GA

- FDA approved
- Post-approval studies underway
- Regional centers of excellence
- $100,000 per implant
- Limited indications
  - Retinal degenerations
  - Light perception vision or worse

Artificial Retina: Retinal Prosthesis

- Video camera
- RF Antenna
- Micro Electrode Array
- Hematoxylin Packaging
- Retina
- Optic Nerve
- Micro Electrode Array
- RF Antenna
- Video camera
How Does Retinal Prosthesis Work?

• Camera records real-time images
• Images are processed by a VPU (video processing unit)
• Signal is sent wirelessly to a coil implanted on the eye wall
• Coil is connected to an electrode array which lies on top of the retina; this must be implanted surgically in one eye
• Electrodes then stimulate remaining retinal cells

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Low Vision

• Low Vision Optometrists & Ophthalmologists
• Low Vision Technicians & Opticians
• Home Health (Occupational Therapists)
• Regional Centers of Excellence
  – Lighthouse
  – VA Medical Center “Boot Camp”
**Intraocular Telescope**

**Conclusions**

- Prevention is important
- Monitoring for disease activity is getting better and easier
- Wet AMD innovations may equal longer duration of action with synergistic therapies & new molecules
- Dry AMD with GA may finally have a treatment available to prevent progression
- Ultimate goal for GA will be to replenish damaged retina
- Low vision innovations help patients cope with deterioration in central vision
Thank you

Special Thanks

- Andrew Moshfeghi, MD, MBA
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