Age Related Macular Degeneration – Current Concepts and Future Directions

Jay M. Haynie, OD, FAAO
Executive Clinical Director – Retina and Macula Specialists

Please silence all mobile devices and remove items from chairs so others can sit. Unauthorized recording of this session is prohibited.
• I am on the advisory board or received honoraria from the following companies:

  Carl Zeiss Meditec
  Arctic Dx – Macula Risk
  Advanced Ocular Care
  Genentech – USMA Lampa Ad Board
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Age Related Macular Degeneration
Age Related Macular Degeneration

- Leading cause of “legal blindness” in person’s over 65.
- Age Dependant:
  - by age 90 ---- 50% will show findings of ARMD
- Women 2x more likely to develop vision loss.
- Smoking substantially increases the risk for severe vision loss.
- Genetic Predisposition
ARMD Is Directly Related To Age

As we grow older, the chance of developing AMD increases

1 Beaver Dam Study
Age Related Macular Degeneration
Risk Factors

- Smoking
- Aging (33% over age 75)
- Family history (up to a 50% lifetime risk vs. up to a 10-12% without)
- Hypertension / Cardiac Disease
- Race (Caucasian females)
- Obesity / high cholesterol
- Sun Exposure
- Low macular pigment
Risk Factors

- Modifiable Risk Factors

- Low Macular Pigment
- Obesity & Poor Diet
- Smoking
- Cardiovascular Disease
Risk Factors

Non-Modifiable Risk Factors

- Family History
- Age
- Gender
Incidence of AMD is increasing

- 5 million new cases per year in Europe & US
- Almost 30 million people in the US have a form of AMD
- More than 7 million have intermediate AMD
- 1.75 million have advanced AMD with vision loss
Clinical Risk Factors: Per Blue Mountains Eye Study

- Large Drusen and Pigmentary change are most predictive for late AMD
- No large drusen or pigmentary changes: <1% of advanced AMD in 5 yrs
- Large Drusen and pigmentary changes: >50% of advanced AMD
There Are Three Stages of AMD

- **Early AMD**
- **Intermediate AMD**
- **Advanced AMD**
  - Choroidal Neovascularization (CNV) – 80%
  - Geographic Atrophy (GA) – 20%
## Intermediate AMD - Prevalence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>4.4 million</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>5.3 million</td>
</tr>
<tr>
<td>Intermediate AMD</td>
<td>7-8 million</td>
</tr>
</tbody>
</table>

The number of people in the U.S. with intermediate AMD far out numbers the number of people with Glaucoma or Diabetic Retinopathy.

15% - 18% of intermediate AMD patients will progress to advanced AMD within 5 years

Source: Arch Ophthalmology, October, 2001
**AMD**

- 80% of pts with AMD will have Dry AMD
- Characterized by RPE disruption, RPE hyperplasia and drusen to varying degrees
- Typically bilateral and fairly symmetrical
- Variable degree of loss of central vision
AMD

- Wet AMD represents only 20% of those with AMD, yet accounts for 90% of patients who are legally blind from AMD.
- Absolutely crucial to differentiate wet from dry!
What’s new in AMD imaging and diagnostic testing?
AngioPlex OCT Angiography from ZEISS

new
non-invasive
microvasculature
imaging technology

AngioPlex OCT Angiography allows visualization of both perfused vasculature and vascular abnormalities of the retina without the need of contrast.
AngioPlex OCT Angiography from ZEISS

**AngioPlex Technology**

AngioPlex Technology detects motion of scattering particles such as red-blood cells within sequential OCT B-scans performed repeatedly at the same location of the retina.

**AngioPlex Maps**

AngioPlex Maps consist of reconstruction of the perfused microvasculature within the retina and choroid.
AngioPlex Color Depth Map

The color depth map combines superficial, deep and avascular retina maps and allows for depth visualization of retinal blood flow.
What’s new in AMD imaging and diagnostic testing?

OCT Angiography
What’s new in AMD imaging and diagnostic testing?

OCT Angiography – blood flow
A comparison to visual fields

- In glaucoma, we talk about pre-perimetric glaucoma
- Is there such thing in AMD?
  - Pre-OCT or Pre-fundus or Pre-FAF AMD
- If there is, what does that mean?
- How do we act?
Dark Adaptation in AMD
(Average 72 year old man)

Staging Test

- Impairment increases with AMD severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rod Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5.7 ± 1.9 minutes</td>
</tr>
<tr>
<td>Early AMD</td>
<td>12.9 ± 6.1 minutes</td>
</tr>
<tr>
<td>High-Risk AMD</td>
<td>16.6 ± 5.2 minutes</td>
</tr>
<tr>
<td>Late AMD</td>
<td>19.0 ± 4.5 minutes</td>
</tr>
</tbody>
</table>

- Odds of having High-Risk AMD increase 11.9% per minute (p = 0.0015)
thickened Bruch’s membrane & drusen → impaired metabolic transport


AMD Pathogenesis
Diagnostic Sensitivity: Patients with known early AMD

- Dark Adaptation
- Contrast Sensitivity
- Photopic Visual Field
- Scotopic Visual Field
- Visual Acuity

Fundus Autofluorescence

Allows us to visualize metabolic changes at the level of the photoreceptors/RPE complex not visualized with standard photography or angiography.
Imaging and AMD

Normal Fundus Autofluorescence
Start to think about this....
Imaging and AMD

Fundus Autofluorescence

Hyper – Autofluorescence =

Increased lipofuscin which is indicative of oxidative stress or injury (ie: DRUSEN)
Imaging and AMD

HYPER Fundus Autofluorescence
Imaging and AMD

Fundus Autofluorescence

\[
\text{Hypo} - \text{Autofluorescence} = \text{Missing or dead RPE cells (ie: atrophy)}
\]
Imaging and AMD

HYPO Fundus Autofluorescence
Courtesy of Heidelberg Engineering
Imaging and AMD

HYPO and HYPER Fundus Autofluorescence
Imaging and AMD

RPE ATROPHY progression over 4 years
Imaging and AMD

Advanced RPE analysis with Cirrus OCT

Tracking of drusen and disease of the RPE as well as atrophy

July 2011

July 2012
Imaging and AMD

The calculated difference does not consider test-to-test variability.

<table>
<thead>
<tr>
<th>RPE Elevation</th>
<th>Prior</th>
<th>Current</th>
<th>Difference</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area in 2 mm Circle (mm²)</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>33.3%</td>
</tr>
<tr>
<td>Area in 5 mm Circle (mm²)</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td>50.0%</td>
</tr>
<tr>
<td>Volume in 3 mm Circle (mm³)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>100.0%</td>
</tr>
<tr>
<td>Volume in 1 mm Circle (mm³)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>100.0%</td>
</tr>
<tr>
<td>Sub-RPE Illumination</td>
<td>Prior</td>
<td>Current</td>
<td>Difference</td>
<td>% Change</td>
</tr>
<tr>
<td>Area in 5 mm Circle (mm²)</td>
<td>12.3</td>
<td>10.1</td>
<td>2.2</td>
<td>45.4%</td>
</tr>
<tr>
<td>Closest distance to Fovea (mm)</td>
<td>0.3</td>
<td>3.1</td>
<td>3.1</td>
<td>infinity</td>
</tr>
</tbody>
</table>
Advanced RPE Analysis: Macular Cube 512x128

Doctor: [redacted]  Signal Strength: [redacted] [redacted]

Prior Visit

Current Visit

RPE Elevation Map

Sub-RPE Slab

RPE Profile™

The calculated difference does not consider test-retest variability.

<table>
<thead>
<tr>
<th>RPE Elevations</th>
<th>Prior</th>
<th>Current</th>
<th>Difference</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area in 3 mm Circle (mm²)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>X%</td>
</tr>
<tr>
<td>Area in 5 mm Circle (mm²)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>X%</td>
</tr>
<tr>
<td>Volume in 3 mm Circle (mm³)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>X%</td>
</tr>
<tr>
<td>Volume in 5 mm Circle (mm³)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>X%</td>
</tr>
<tr>
<td>Sub-RPE Illumination</td>
<td>Prior</td>
<td>Current</td>
<td>Difference</td>
<td>% Change</td>
</tr>
<tr>
<td>Area in 3 mm Circle (mm²)</td>
<td>2.7</td>
<td>3.3</td>
<td>0.6</td>
<td>14.8%</td>
</tr>
<tr>
<td>Closed distance to Fovea (mm)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>X%</td>
</tr>
</tbody>
</table>
Advanced RPE Analysis: Macular Cube 512x128

**Prior Visit**

- RPE Elevation Map
- Sub-RPE Slab
- RPE Profile™

**Current Visit**

- RPE Elevation Map
- Sub-RPE Slab
- RPE Profile™

**Table:**

<table>
<thead>
<tr>
<th>RPE Elevation</th>
<th>Prior</th>
<th>Current</th>
<th>Difference*</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area in 3 mm Circle (mm²)</td>
<td>5.2</td>
<td>5.3</td>
<td>0.1</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*The calculated difference does not consider test-retest variability.*
8/8/2017

68 year old with AMD and new vision loss OD

Imaging and AMD

Prior Visit

Current Visit

RPE Elevation Map

Sub-RPE Slab

RPE Profile™
Imaging and AMD

*Drusen and drusenoid PED’s*
Imaging and AMD

Pigment Epithelial Detachment (PED)

Vitelliform lesions
Imaging and AMD

Contour Maps
Imaging and AMD

Retinal Pigment Epithelial Atrophy
Imaging and AMD

Choroidal Neovascular Membrane (CNV)

- associated with an alteration of the RPE with an accumulation of subretinal fluid or CME
Imaging and AMD

Choroidal Neovascular Membrane (CNV)
74 year old woman with AMD
74 year old woman with AMD

Fluorescein Angiography Images
74 year old woman with AMD

Angioplex Images
AngioPlex versus FA imaging
(CB) 68 year old man with sudden central vision loss
(CB) 68 year old man with sudden central vision loss
(CB) 68 year old man with sudden central vision loss
(CB) 68 year old man with sudden central vision loss
AMD Cases
Pigment Epithelial Detachment
AMD Cases – Pigment epithelial detachment
AngioPlex reveals no blood flow
AMD Cases – Post anti-VEGF treatment
AMD Cases – Post anti-VEGF treatment
Is AMD in your DNA?
AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk.

In other words: AMD is >70% due to genetics!

J.M. Seddon, B Rosner et al; IOVS May 2009
Is Advanced AMD in your DNA?

First degree relatives of people affected by AMD are at significantly increased risk of AMD.
Major genetic factors

- **CFH**
  - Single most important genetic component
  - CHF Y402H
- **ARMS2/HTRA1**
  - Second most important gene in AMD
- **C3**
  - Another component of the complement system
- **ND2**
  - Mitochondrial oxidative phosphorylation molecule
Genetic Factors and Risk: More than additive!

- Former Smokers: 1.29x
- Current Smokers: 2.4X
- Non-Smoker and CFH,Y402H: 7.6X
- Current smoker and CFH,Y420H: 34X
CFH

- Knowledge of genetic risk is important
  - Increased counseling for patients at high risk
  - Know which pts need to be screened more frequently
  - Sooner vitamin supplementation
  - May have implications regarding treatment
    - 37% higher risk of additional Lucentis injections if CFH Y402H
    - CFH TT/TC treated with Avastin had increase in vision with 53.7% improved vs. only 10.5% if CC genotype
Macula Risk® NXG

THE NEXT GENERATION OF AMD GENETIC TESTING
Taking a sample:

Collect cells by brushing cheek firmly with the swab *20x* over the entire inside of *one* cheek:
- Avoid the gum line
- It is recommended that the patient not consume food or coffee for 30 minutes prior to collection
Labels and Shipping

Fill out the Patient’s Name and D.O.B. on the 3rd and 4th barcode labels.

Adhere completed labels to swab sleeves.
Labels and Shipping

Place both labelled swab sleeves into the biohazard bag and seal completely.
Packaging and Shipment

Place the following items into a padded shipping envelope and seal:

- Biohazard bag with swabs
- **White** copy of completed TRF
- **Front and back** copies of patient’s insurance cards (primary and secondary)
Labels and Shipping

Adhere the prepaid and pre-addressed USPS shipping label to the front of the sealed envelope.
Labels and Shipping

Have samples ready for your USPS carrier to pick up, or deliver them to the nearest USPS drop box.

Ship samples at least weekly.
Reporting

Sample is shipped to Arctic Medical Laboratories where the test is performed.
Reporting

Reports will be FAXED to the office about 3 weeks after submission

A color copy will then be MAILED to the office as well
IMPORTANT!

Your test results will be delayed if

- Any information on the form is missing
- The insurance information is missing
- The barcodes are not completed and attached to the swab sleeves
Patient Report:

Genes Tested

Eye Exam
BMI and Smoking

Risk for Advanced AMD

Macula Risk Score

Macula Risk Score

Macula Risk Score

Macula Risk Score

RETINA & MACULA SPECIALISTS

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**Patient Report:**

**Genes Tested**

**Eye Exam**
**BMI and Smoking**

**Risk for Advanced AMD**

**Macula Risk Score**

---

**Arctic Medical Laboratories**

**Accession Number:** AMN55-005014

**Patient Name:**

**Date of Birth:**

**Gender:**

**Date:**

**Age:**

**Height/Weight:**

**BMI:**

**Smoking Status:**

**Macular Risk Score**

---

**Retina & Macula Specialists**
Highest Risk (Include other factors)

Patient profile:
- Age greater than 65;
- Present with Drusen;
- Macula Risk Score 3, 4 or 5.

Should be monitored more than once / year

<table>
<thead>
<tr>
<th>Macula Risk Score</th>
<th>Risk of GA or CNV (%)</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Low)</td>
<td>0-5</td>
<td>49.6</td>
</tr>
<tr>
<td>2 (Average)</td>
<td>6-15</td>
<td>30.6</td>
</tr>
<tr>
<td>3 (Increased)</td>
<td>16-40</td>
<td>16.6</td>
</tr>
<tr>
<td>4 (High)</td>
<td>40-55</td>
<td>2.2</td>
</tr>
<tr>
<td>5 (Very High)</td>
<td>55 – 96.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Genetics of AMD and supplementation

Ophthalmology
Available online 21 August 2013
In Press, Corrected Proof — Note to users

CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

Carl C. Awh, MD1, Anne-Marie Lane, MPH2, Steven Hawken, MSc3, Brent Zanke, MD, PhD4,5, Ivana K. Kim, MD2
Genetic Testing for Supplements – WHY?

AMD Patients

- Antioxidants*
  - 17% risk reduction

- Zinc Oxide
  - 21% risk reduction

- Antioxidants* + Zinc Oxide
  - 25% risk reduction

AREDS Study (2001)
Risk reduction in developing advanced disease, as compared to placebo

Genetic Variation Determines Treatment
Overall AREDS Response is modestly positive

*Heterogeneous response to zinc/antioxidants within AREDS Category 3 patients*
Summary

1. More than Five publications point to a problem with Zinc in high risk CFH patients
2. One paper with awkward statistical modeling says there is no effect but it also shows no effect for AREDS
3. At least 13% of patients had a result with AREDS that was worse than placebo;
4. Normally any one study demonstrating toxicity of this magnitude stops the use of therapy.
Options to consider

1. Continue to give AREDS to everyone with Category 3 Disease

2. Do nothing – no one gets AREDS

3. Test patients for optimal treatment and counsel for compliance
Personalized Medicine

AREDS for all AMD patients

25% risk reduction.
What happened to the other 75%
First do no harm…. 

- Zinc can cause harm/prevent benefit to some….potentially determined by genetics  
  Individualize care based on genotype  
  (not just phenotype) 

- The dawn of pharmacogenetics in eyecare!
For 23% of patients, the AREDS formulation was the best treatment.

49% of patients derive more benefit from a formulation other than AREDS.

For 15-20% of the patients the AREDS combination was harmful and accelerated vision loss significantly faster than placebo.
Example:

- What would you recommend for this patient?

*Not so fast, don’t you want to know genetics?*
How do you calculate vitamin risk?
So, for this patient

![Ocular Vitamin Pharmacogenetic Calculator](image)

**Ocular Vitamin Pharmacogenetic Calculator**

Enter the patient's genotype for the following SNPs:

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>CC</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>CC</td>
</tr>
<tr>
<td>ARMS2</td>
<td>372_815del443ins54</td>
<td>Wildtype (NN)</td>
</tr>
</tbody>
</table>

**Vitamin Recommendation:** Antioxidants without Zinc
But could have been

Individualized analysis and treatment is what each patient deserves

- Have to use both phenotype and genotype in determining best supplements and follow up
Personalized Medicine

- Each of your patients is an individual with their own potential needs
Nutrition

- So much to say, so little time, so I will keep it brief:
- AREDS showed that supplementation worked for moderate/advanced dry AMD
- AREDS2 showed the same
If you don’t think your patients are thinking about and/or taking ocular supplements...
# Eye Vitamins Own 2 of the Top 10 Vitamin Category SKUs

<table>
<thead>
<tr>
<th>Rank</th>
<th>SKU Description</th>
<th>$ Sales (000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mega Red Omega 3 60ct</td>
<td>$34,301</td>
</tr>
<tr>
<td>2</td>
<td>Lipozene 30ct</td>
<td>$32,593</td>
</tr>
<tr>
<td>3</td>
<td>Align Probiotic 28 ct</td>
<td>$28,421</td>
</tr>
<tr>
<td>4</td>
<td>Centrum Silver Ultra Women’s 100ct</td>
<td>$27,357</td>
</tr>
<tr>
<td>5</td>
<td>Centrum Silver 125ct</td>
<td>$27,234</td>
</tr>
<tr>
<td>6</td>
<td>Airborne 10ct</td>
<td>$26,578</td>
</tr>
<tr>
<td>7</td>
<td>Ocuvite Adult 50+ 50ct</td>
<td>$26,133</td>
</tr>
<tr>
<td>8</td>
<td>PreserVision AREDS Soft Gels 120ct</td>
<td>$25,802</td>
</tr>
<tr>
<td>9</td>
<td>Align Probiotic 42ct</td>
<td>$25,088</td>
</tr>
<tr>
<td>10</td>
<td>Phillips Colon Health 30ct</td>
<td>$23,588</td>
</tr>
</tbody>
</table>

Source: Nielsen XAOC 52 weeks ending May 11, 2013
Stop the madness

• Prescription (EXACT RECOMMENDATION) to patient for local acquisition

• Direct distribution that is shipped to pt

• Stock and sell directly to patient

• Guide patient to specific Web site/telephone #

Samples are always a good idea
# Genotype Directed Eye Vitamin Formulations

## 10 Manufacturers of AREDS Formulations for Macula Risk

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Doctors Optimal Formula</td>
<td><a href="http://www.doctorsoptimalformula.com">www.doctorsoptimalformula.com</a></td>
</tr>
<tr>
<td>2  Fortifeye Vitamins</td>
<td><a href="http://www.fortifeye.com">www.fortifeye.com</a></td>
</tr>
<tr>
<td>3  MacuHealth</td>
<td><a href="http://www.macuhealth.com">www.macuhealth.com</a></td>
</tr>
<tr>
<td>4  Pure Encapsulations</td>
<td><a href="http://www.purecaps.com">www.purecaps.com</a></td>
</tr>
<tr>
<td>5  Macular Health</td>
<td><a href="http://www.macularhealth.com">www.macularhealth.com</a></td>
</tr>
<tr>
<td>6  VisiVite</td>
<td><a href="http://www.visivite.com">www.visivite.com</a></td>
</tr>
<tr>
<td>7  iRx</td>
<td><a href="mailto:bethany@retinahealthcenter.com">bethany@retinahealthcenter.com</a></td>
</tr>
<tr>
<td>8  Doctors Advantage</td>
<td><a href="http://www.doctorsadvantage.net">www.doctorsadvantage.net</a></td>
</tr>
<tr>
<td>9  Vitamin Health</td>
<td><a href="http://www.viteyes.com">www.viteyes.com</a></td>
</tr>
<tr>
<td>10 Zeavision</td>
<td><a href="http://www.eyepromise.com">www.eyepromise.com</a></td>
</tr>
</tbody>
</table>
There have been some recent studies worth being aware of

- Might aspirin have negative affect on the incidence of Wet AMD?
  - Liew et al. JAMA. ASA and AMD
  - Klein et al. JAMA. ASA and AMD

- Might Fish oil cause cancer?

- Is Fish oil beneficial to health?
  - AREDS2: JAMA IM online 3/14 no benefit to CV endpoints
    These affect patient perceptions!
The AMD Problem
STILL today

Wet AMD
Initial Presentation
First Eye
80% are Blind
(20/200 or worse)
Excellent results in the second eye need to be duplicated in patients’ first eyes
Medical Utility – Why Should We Test?

- Early detection can save sight
- Genetics helps identify patients at risk of progression
- More frequent monitoring of high risk patients leads to earlier treatment and better visual outcomes
AAO PPP Guidelines for AMD

- For patients over 65 with no risk factors a comprehensive exam performed every 1-2 years seems to offer a reasonable approach for detection.

- For Early AMD a return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of wet AMD.

- For Intermediate AMD a return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of wet AMD.

- Patients at exceptionally high risk may be examined more frequently in an effort to detect asymptomatic CNV at a treatable stage.

*American Academy of Ophthalmology Preferred Practice Pattern – Age related Macular Degeneration 2008*
AOA Guidelines Similar

- Over age 55 with two or more risk factors should have an annual eye examination.
- Depending upon risk, patients with hard drusen or pigmentary changes should be seen every 6-12 months and receive an Amsler grid with instructions.
- Patients with high risk, soft confluent drusen and/or granular pigmentary degeneration should be seen every 4-6 months and receive an amsler grid with instructions.
- Patients with geographic atrophy should be seen every 6-12 months, depending upon the extent of atrophy.

American Optometric Association Clinical Practice Guidelines – Care of the Patient with AMD 2004
Working Together to set a New Standard

- Retina Specialist
- Primary Eye Care Professional

Leadership and Education
Early Detection and Referral
Once diagnosed with Exudative Wet AMD, treatment will be needed...
The Catt is out of the bag…

- CATT: Comparison of Lucentis monthly vs Lucentis PRN vs Avastin monthly vs Avastin PRN
- Bottom line:
  - Lucentis essentially equal to Avastin in outcome measures
  - Lucentis essentially equal to Avastin in Adverse events: both relatively low
  - Avastin has significant economic benefits!

Cost implications

**Avastin per year**
- Cost per injection: $50
- Monthly/yr: $600
- PRN: $350

- 250,000 Americans:
  - Monthly/yr: 150,000,000
  - PRN/yr: 87,500,000

**Lucentis per year**
- Cost per injection: $2000
- Monthly/yr: $24000
- PRN: $14000

- 250,000 Americans:
  - Monthly/yr: 6,000,000,000
  - PRN/yr: 3,500,000,000
Side effects
- 40% Avastin vs 32% Lucentis

Non-central GA was noted more often in LUCENTIS q1M group vs Avastin prn group, which will interfere with reading
- 26% lucentis q1M
- 12% avastin PRN
Great news for our patients and economy, but....

- Does CATT change the way we practice?
- Does it change our primary focus???

- Ideally, nobody would need Avastin or Lucentis!

Avastin, Eylea and Lucentis sound great, so where do we fit in ......
The best way to achieve a good treatment outcome is not to need that treatment! It is the only way to achieve 100% efficacy!
Referral Patterns for Optometry

Treat and Extend (TREX) Concept

New Diagnosis of Neovascular AMD = Induction Phase
  then 4 week follow up – if “dry” – treat
  then 6 week follow up – if “dry” – treat
  then 8 week follow up – if “dry” – treat
  then 10 week follow up – if “dry” – treat
  then 12 week follow up – if “dry” – follow

This will aid in determining the frequency of injections for an individual patient and identify the risk interval.
Complications of Intravitreal Injections and high risk patients

Patients with a large pigment epithelial detachment (PED) secondary to AMD prove challenging to manage

It's about RISK versus BENEFIT
Intravitreal Injections: What We Must Know!

Complications of Intravitreal Injections
Tear or Rip of the RPE
Intravitreal Injections: What We Must Know!

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Intravitreal Injections: What We Must Know!
Complications of Intravitreal Injections
Tear or Rip of the RPE
What about long-term Lucentis follow up….

Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON

A Multicenter Cohort Study (SEVEN-UP)

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Not such a rosy bottom line..

**standard error of the mean**

*p<0.05 vs SEVEN-UP Year 7.3*

**p<0.0001 vs SEVEN-UP Year 7.3**

***p<0.001 vs SEVEN-UP Year 7.3***
Intravitreal Injections: What We Must Know!

Referral Patterns for Optometry

Does excessive anti VEGF lead to geographic atrophy (GA)

2011  2014  2015
How do you know if a drug works? When Wall Street likes the company that makes it!!
What is the newest approved Anti-VEGF for AMD?
VIEW1 and VIEW2: approval of Eylea

Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

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Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye: Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

Design: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

Participants: Patients (n = 2418) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

Intervention: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

Main Outcomes Measures: The primary end point was noninferiority (margin of 10%) of the aflibercept regimen to ranibizumab in the proportion of patients maintaining vision at week 52; Boening et al letters on Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

Results: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.0%, 95.3%, and 95.0%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

Conclusions: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

Financial Disclosures: Proprietary or commercial disclosure may be found after the references. Ophthalmology 2012;119:2037-2046 © 2012 by the American Academy of Ophthalmology.
Eylea

- Eylea given for Wet AMD .5mg monthly, 2mg monthly, 2mg q2mos vs Lucentis monthly in >2400
- Primary outcome measure of stable vision
  - 95% vs 96% vs 91% vs 95%
What will be the next frontier
What will be the next frontier

- In Anti-VEGF it will be topical and oral treatments
  - Both are in trials and showing promise
- Longer acting or sustained release delivery methods
- Newer drug classes
  - Complement factor inhibitors
  - Your imagination may fill in the blank…
Age Related Macular Degeneration

Clinical Trials...........

**Dry AMD**
- Acucela (oral) FDA did not approve in 2016
- MacuCLEAR (topical)
- Lampalizumab (intravitreal)

**Wet AMD**
- Fovista (intravitreal)
- Squalamine Lactate (topical)
Age Related Macular Degeneration

Clinical Trials………. DRY

♦ MacuCLEAR 1% Ophthalmic solution

♦ Strong vasoactive drug which is intended to increase choroidal blood flow

♦ Currently in Phase II/III clinical trials
Age Related Macular Degeneration

Clinical Trials……….. DRY

♦ Lampalizumab for intravitreal injection

♦ Complement D Inhibition

♦ MOHALO study results a 20.4% reduction in geographic atrophy over 18 months as compared to controls
Age Related Macular Degeneration

Clinical Trials........... WET

- **Fovista for intravitreal injection**

- **Fovista acts against platelet derived growth factor (PDGF) which stimulates blood vessel growth in AMD.**

- **Current intravitreal treatment acts against vascular endothelial growth factors (VEGF)**
Subretinal fibrosis (disciform scarring) is one of the most frustrating components of exudative AMD and current compounds do not mitigate against this.

Fovista targets this complication and is being used in conjunction with anti VEGF in trials.

Currently in Phase III clinical trials.
Age Related Macular Degeneration

Clinical Trials.......... WET

♦ Fovista for intravitreal injection

♦ Patients receiving Fovista in conjunction with Lucentis had an additional 62% additional benefit from baseline acuity as compared to Lucentis monotherapy.
Age Related Macular Degeneration

Clinical Trials........... WET

♦ Squalamine Lactate – Ophthalmic Solution

♦ Topically applied anti-angiogenic drug that acts against the development against neovascularization through inhibition of multiple growth factors of angiogenesis, including VEGF, PDGF and basic fibroblast growth factor (bFGF)
Age Related Macular Degeneration

Clinical Trials........... WET

♦ Squalamine Lactate – Ophthalmic Solution

♦ Currently in clinical trials
  ♦ Squalamine BID with Lucentis
  ♦ Placebo BID with Lucentis

♦ Early results reveal a decrease in the number of Lucentis injections vs placebo
OD’s moving forward

- Exciting times for AMD patients
- Exciting times for OD’s in caring for patients
- OD’s likely to be more involved as treatment modalities change over time
- Today’s thoughts will be obsolete tomorrow, so we need to keep up (for the sake of our patients!)
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