Age Related Macular Degeneration

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Disclosures

- I am on the advisory board or received honoraria from the following companies:
  - Arctic Dx, Thrombogeneics, Carl Zeiss Meditec, Notal Vision, Reichert

These affiliations will have no effect on the content of this lecture

Age Related Macular Degeneration
**Age Related Macular Degeneration**

- Leading cause of “legal blindness” in persons 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

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**ARMD Is Directly Related To Age**

As we grow older, the chance of developing AMD increases

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**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

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

- Over 60?
- Over 70?
- 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

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?

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>
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<tr>
<td>Normal</td>
<td>5.7 ± 1.9 minutes</td>
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<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>
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- Odds of having High-Risk AMD increase 11.9% per minute (p = 0.0015)

Diagnostic Sensitivity:

Patients with known early AMD

Akin to stress test in cardiology... rest and then try to perform...


Imaging and AMD

Fundus Autofluorescence

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

Hyper - Autofluorescence =

Increased lipofuscin which is indicative of oxidative stress or injury (ie: DRUSEN)
HYPER Fundus Autofluorescence

HYPO Fundus Autofluorescence

Fundus Autofluorescence

Hypo – Autofluorescence =

Missing or dead RPE cells (ie: atrophy)

HYPO Fundus Autofluorescence

Courtesy of Heidelberg Engineering
Imaging and AMD

Retinal Photo

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
Advanced RPE Analysis of Drusen
68 year old with AMD and new vision loss OD

Imaging and AMD
**Imaging and AMD**

Choroidal Neovascular Membrane (CNV) - associated with an alteration of the RPE with an accumulation of subretinal fluid or CME

**Is AMD in your DNA?**

Genes add Predictive Power

AUC – ROC 'C' Statistic Scores (AREDS 2 & 3)

1. Toss a Coin = 0.5 (Baseline)
2. Eye Exam + Age = 0.732 (+46.4%)
3. Eye Exam + Age + BMI + Smoking = 0.757 (+10.7%)
4. Add Genetics = 0.8221 (+24.9%)

Genetic Testing adds 24.9% improvement

\[
\frac{0.821-0.757}{0.757-0.5} \times 100 = 24.9\%
\]

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

Major genetic factors
- CFH
  - Single most important genetic component
  - CFH 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 33.7% improved vs. only 10.5% if CC genotype

Macula Risk® NXG

THE NEXT GENERATION
OF
AMD GENETIC TESTING

Nicox - RetnaGene

DNA testing: How it works
Patient Report:

Genes Tested

Risk for Advanced AMD

Eye Exam, BMI and Smoking

Macula Risk Score

Macula Risk Score

Genetics of AMD and supplementation

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

Genetic Testing for Supplements – WHY?

AMD Patients

Antioxidants

Zinc Oxide

Antioxidants + Zinc Oxide

17% risk reduction

21% risk reduction

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

Genotype Group

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<tr>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Better</td>
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<td>Worse</td>
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<td>Average</td>
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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
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!

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

- 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?

Genotype Directed Eye Vitamin Formulations

10 Manufacturers of AREDS Formulations for Macula Risk

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<tr>
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www.macularisk.com
The AMD Problem
STILL today

Wet AMD
Initial Presentation
First Eye
80% are Blind
(20/200 or worse)

Save the First Eye

- Excellent results in the second eye need to be duplicated in patients’ first eyes

If 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

**CATT**

- 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
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)

Not such a rosy bottom line..

What is the newest approved Anti-VEGF for AMD?
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

- 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..........  
- Acucela – ACU-4429 is an oral drug in clinical trials for the treatment of geographic atrophy in AMD.  
- Acucela is thought to relieve the metabolic stress on the retina whereby reducing the accumulation of toxic byproducts, such as A2E, which is recognized as a contributor to the progression of atrophic disease.

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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