Age Related Macular Degeneration – Current Concepts and Future Directions

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Dedicated to excellence in care for the back of the eye.

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Disclosures

- I am on the advisory board or receive honoraria from the following companies:
  - Arctic Dx, Carl Zeiss Meditec, Advanced Ocular Care, Genentech – Lamp Advisory

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

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

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

ARMD Is Directly Related To Age

As we grow older, the chance of developing AMD increases

1 Beaver Dam Study

55 to 64 12%
65 to 74 16%
Over 75 30%
Incidence of AMD is increasing

- 1.5 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

There Are Three Stages of AMD

- Early AMD
- Intermediate AMD
- Advanced AMD

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

**Chance of Progressing to Advanced 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 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

- Consist of reconstruction of the perfused microvasculature within the retina and choroid.
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)

<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)
**AMD Pathogenesis**

- Thickened Bruch’s membrane & drusen → Impaired metabolic transport


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**Diagnostic Sensitivity: Patients with known early AMD**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark Adaptation</td>
<td>95%</td>
</tr>
<tr>
<td>Contrast Sensitivity</td>
<td>80%</td>
</tr>
<tr>
<td>Scotopic Visual Field</td>
<td>70%</td>
</tr>
<tr>
<td>Scotopic Visual Field</td>
<td>60%</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>50%</td>
</tr>
</tbody>
</table>

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**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.

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**Start to think about this….**

**Fundus Autofluorescence**

*Hyper / Autofluorescence =*

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

Fundus Autofluorescence

Hypo - Autofluorescence =

Missing or dead RPE cells (ie: atrophy)

Imaging and AMD

RPE ATROPHY progression over 4 years

Advanced RPE analysis with Cirrus OCT

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

July 2011

July 2012
68 year old with AMD and new vision loss OD

Drusen and drusenoid PED’s

Pigment Epithelial Detachment (PED)

Vitelliform lesions

Contour Maps

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

74 year old woman with AMD

Fluorescein Angiography Images

AngioPlex versus FA imaging
(CB) 68 year old man with sudden central vision loss

AMD Cases
Pigment Epithelial Detachment

AngioPlex reveals no blood flow
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?

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

Knowledge of genetic risk is important
- Increased counseling for patients at high risk
- Know which pts need to be screened most 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 increased vision with 53.7% improved vs. only 10.5% if CC genotype

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Macula Risk® NXG
THE NEXT GENERATION OF AMD GENETIC TESTING

DNA testing: How it works

DNA Collection Process

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

68

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.

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

Ship samples at least weekly.

Labels and Shipping

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

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?

Overall AREDS Response is modestly positive

Heterogeneous response to zinc/antioxidants within AREDS Category 3 patients

Genetic Variation Determines Treatment
**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!

**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?
How do you calculate vitamin risk?

But could have been

Personalized Medicine

Nutrition

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>$32,993</td>
</tr>
<tr>
<td>3</td>
<td>Align Probiotic 28 ct</td>
<td>$29,421</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>$25,008</td>
</tr>
<tr>
<td>10</td>
<td>Phillips Colon Health 30ct</td>
<td>$23,588</td>
</tr>
</tbody>
</table>

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 Fortifye Vitamins</td>
<td><a href="http://www.fortifye.com">www.fortifye.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 Vixiye</td>
<td><a href="http://www.vixiye.com">www.vixiye.com</a></td>
</tr>
<tr>
<td>7 IRV</td>
<td>bethany@retinashccentercom</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.vitamineyes.com">www.vitamineyes.com</a></td>
</tr>
<tr>
<td>10 ZeaVision</td>
<td><a href="http://www.eyezea.com">www.eyezea.com</a></td>
</tr>
</tbody>
</table>

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

Once diagnosed with Exudative Wet AMD, treatment will be needed…
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.

Intravitreal Injections: What We Must Know!
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

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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)

Sona Rafii, MD, MPH,1 Robert B. Bhesani, MD, PhD,1 David S. Beaver, MD,2 SimViz R. Saad, MD,3 Kang Zhang, MD, PhD,4 for the SEVEN-UP Study Group
Not such a rosy bottom line..

Intravitreal Injections: What We Must Know!

Referral Patterns for Optometry
Does excessive anti VEGF lead to geographic atrophy (GA)

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

Dry AMD
MacuCLEAR (topical)
Lampalizumab (intravitreal)

Wet AMD
Squalamine Lactate (topical)

Clinical Trials………..

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

**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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