Age-related Macular Degeneration Update

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Financial Disclosures
- Honoraria
  - VSP
  - Merck
- Review of Optometry
- Optometric Management
- Paid Advisory Board Member
  - Carl Zeiss Meditec
  - Zeiss Vision
  - Thrombogenics
  - Nites
- Consulting Fees
  - Carl Zeiss Meditec

AMD Update 2016

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Financial Disclosures
- CE Companies
  - CEInItaly.com
  - EyeSkiUtah.com
- Proprietary Interests
  - None

QUESTIONS AND COMMENTS?
Course Goals

- To provide useful clinical information about AMD
- Prevention
- Early Diagnosis
- Treatment and management

What are the 4 retinal pigments?

- Lutein/Zeaxanthin – found in the macula’s sensory layers
- Melanin – found in the RPE
- Lipofuscin – found in the RPE

About AMD

- "Dry" (Drusen, RPE clumping, RPE atrophy)
- "Wet" (CNVM)

"Dry" ARMD = 90% of all cases
"Wet" ARMD = 10% of all cases
(90% of all cases of severe vision loss)

Advanced Atrophic AMD

Advanced Neovascular AMD
Both Wet and Dry (Advanced)

**The Problem**

- The AMD "Epidemic"
- AMD is the leading cause of blindness in individuals over the age of 50 in the developed world.

**The Burden of Disease**

**Prevalence of Ocular Diseases**
- Glaucoma: 4 million
- Diabetic Retinopathy: 5 million
- Intermediate AMD: 8 million

**Epidemiology**
- 2004 data: 15 million affected in the United States
- 2012 data estimates 17 million
- Projection for 2016 is 20 million

**Distribution (age)**
- 55-64: 17% of Caucasians have drusen/AMD
- 65-74: 26%
- >75: 42%

1. Age-Related Eye Disease Study 1 data
**AMD: A Changing Environment**

- How will these dramatic changes and projections impact your practice?

**Terminology**

- Age Related Maculopathy (ARM)
  - age related changes in central retina
  - Examples: drusen, RPE disturbances
- Age Related Macular Degeneration (AMD)
  - retinal status when vision deteriorates

**What is AMD?**

- Continuum of Normal Aging and Disease
- Degenerative changes are observed in maculae of most elderly persons to some degree.

**Classification of AMD**

- **Non-exudative (atrophic, “dry”)**
  - Can be performance-degrading
  - Majority of AMD cases
- **Exudative (neovascular, hemorrhagic, “wet”)**
  - Choroidal NV—devastating to central VA
  - Minority of AMD cases
“Dry AMD is the new Wet AMD”

Carmen Puliafito, MD, Dean of the Keck School of Medicine of USC

The AMD “Epidemic”

How should we as optometrists respond?

Prevention
Early Diagnosis
Early Intervention
Improved Visual Outcomes

Questions, Comments, Stories?

Projected Prevalence of Advanced AMD* in the United States


Advanced AMD starts out like this:

Large, ill-defined, and confluent soft drusen**

Intermediate Stage AMD

- AREDS Category 3
- Extensive intermediate drusen (63-124μ diameter)
- At least one large druse (>125μ)
- Geographic atrophy not involving the foveal center

**Soft drusen: Large, ill-defined, and confluent
Unfavorable prognostic signs leading to CNVM, GA:

- Soft, large, confluent drusen
- Reticular (pseudo)drusen
- Focal hyperpigmentation
- Disciform lesion in the fellow eye
- Older age

Fluorescein Angiography (FA)

- FA answers the question: is the blood-retinal barrier intact?

FA

- The "gold standard" for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients.

Conversion to Exudative AMD

**20% of dry (non-exudative) AMD eyes progress to wet (exudative) AMD.

**Indocyanine green (ICG) is a dye that is used as an alternative to fluorescein.
Advanced AMD

- Defined as either:
  - Geographic atrophy (GA)
  - Atrophy of the RPE and/or photoreceptors, CC
  - "End-stage" non-exudative (dry) AMD
  - Choroidal neovascularization (CNV)
  - Exudative "wet"
- 80-90% of advanced AMD cases are due to CNV.

CNVM Size and Progression

Average size CNV lesion @ diagnosis 3000-3300µm

Growth = ~ 10-20 µm/day

Too large, too late

Olsen, TW. Ophthalmology Feb. 2004

CNV ---> FV Scar

AMD and Drusen

- AMD is a disease resulting from poor "Waste Management".
- Drusen are "pockets of inflammation"
  - Recent investigations show that proteins associated with inflammation and immune-mediated processes are prevalent among drusen-associated constituents.

Drusen

Drusen is the earliest clinically detectable feature of AMD.**
**The "gold standard" for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients is Fluorescein Angiography.**

Current commercially available Spectral Domain OCT is capable of obtaining 3-5um resolution**

**The earliest clinically detectable feature of AMD is Drusen.**

Reticular (Pseudo)drusen (RPD)

- Seen as a reticular pattern of small yellow-white lesions often in the superior macula, RPD are a high-risk sign for advanced AMD.
**Current commercially available Spectral Domain OCT is capable of obtaining 3.5 um resolution**

**Autofluorescence (FAF)**

- **Principle**: When stimulated with light in the blue range, lipofuscin granules emit yellow fluorescence.
- **Patterns of fundus autofluorescence may predict which cases will progress more quickly.**
Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites

Reduced degradation of cellular debris leads to the accumulation of lipofuscin, toxic vitamin A metabolites.

Autofluorescence

Fundus Autofluorescence

Wet AMD
**Blue Peak™ Applications - Wet AMD**

- Hyperfluorescence in FAF
- FA 36 sec
- FA 69 sec

**Imaging**

- Adaptive Optics
- En face OCT angiograms

**Multi-Modality Imaging**

- Infrared
- Red-free
- BluePeak™ - blue laser autofluorescence
- Fluorescein Angiography
- Indocyanine Green Angiography
- Spectral-Domain OCT
- Color photography

**BluePeak™ - Blue Laser Autofluorescence**

- Multi-modality imaging: BluePeak + SD-OCT
- Offers new perspective of the structure-function relationship within the retina

**Simultaneous FAF and OCT**

- Geographic Atrophy

  - FAF shows areas of hypo-autofluorescence in GA
  - OCT outlines the corresponding photoreceptor dropout

**Questions & Comments?**
Genetics and AMD

- Inherited variation in the complement factor H gene is a major risk factor for drusen.
- A single-nucleotide polymorphism (SNP) in the promoter region of HTRA1 (a serine protease gene on chromosome 10q26) is a major risk factor for Wet AMD.
- DeWan, A. Science, November 2006: Vol. 314. no. 5801, pp. 989 - 992

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Naturally occurring variations conferring AMD risk
Smoking interacts with CFH Gene variants to increase AMD risk by 5X compared with genetically similar nonsmokers.


Example of Genomics

AMD Gene Associations

- Mutations in the TIMP3 gene
- Metalloproteinase inhibitor 3 gene
- Two variants involved in the HDL cholesterol pathway.
- Human hepatic lipase (LIPC) and cholesterol ester transfer protein (CETP).
- Proceedings of the National Academy of Sciences (4/2010)

Parallel Worlds: Heart Disease and AMD

- Diet – Low fruit/vegetable consumption increases risk of AMD and CVD
- Obesity and physical inactivity
- C-reactive protein (elevated)
  - Inflammatory marker
- Homocysteine (elevated)
- Omega-3 EFA may be beneficial for AMD patients
- Cholesterol (elevated)
- Serum Iron – Increased amounts may increase AMD and CVD

AMD: a sick eye in a sick body?

Johanna Seddon, MD (Tufts U)

“Don’t smoke; follow a healthful diet rich in dark green leafy vegetables and low in fat; eat fish a few times a week; maintain a normal weight and waist size; exercise regularly; and control blood pressure and cholesterol.”

“Anyone with signs of intermediate-level macular degeneration in both eyes or advanced macular degeneration in one eye should also take dietary supplements that contain lutein, zeaxanthin, vitamin C, vitamin E, and zinc.”
The Complement Cascade: Inflammation

A BMI over 30 increases AMD risk by 2.5X.

Example of Genomics

Clinical & Experimental Ophthalmology

Nutritional Factors

AREDS 1 and 2

Key AMD-associated Genes

To whom should we recommend genetic testing to predict progression to advanced AMD?
AREDS 1

AREDS 1 Grading Scale

1. No drusen or a few small drusen.
2. Pigment abnormalities or non-extensive small or intermediate drusen.
3. Extensive intermediate drusen or any large drusen or non-central atrophy.
4. Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovascularization or geographic atrophy).

Retina Quiz

The AREDS 1 study found that in subjects with intermediate AMD, or advanced AMD in one eye (but not the other):

a. Zinc alone lowered risk of advanced AMD by about 25 percent.

b. Lutein alone lowered risk of advanced AMD by about 25 percent.

c. Antioxidants increased risk of advanced AMD by about 25 percent.

d. Antioxidants + zinc lowered risk of advanced AMD by about 25 percent.
"AREDS 1 resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by 25% at 5 years."

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland

AREDS 2: Purpose

- To determine if adding lutein/zeaxanthin, omega-3s, or a combination could improve upon the positive results found in the AREDS 1.
- To evaluate the effect of eliminating beta carotene, lowering zinc, or both.

4203 participants aged 50 to 85 with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye. (AREDS Categories 3 and 4)
AREDS 1 and 2 Formulations

- Vitamin C: 500 mg*
- Vitamin E: 400 IU*
- Beta-carotene: 15 mg (May be listed on the label as “25,000 IU vitamin A as beta-carotene”) (eliminated)
- Why?
- Zinc oxide: 80 mg (40 mg)
- Why?
- Copper: 2 mg (needed to prevent Cu deficiency caused by high dosage of zinc)*
- Lutein & Zeaxanthin (10 mg & 2 mg)
- Omega-3 fatty acids (1 gram)

AREDS 2 Design

- 4203 participants were randomized to placebo with no additional supplementation or to 1 of 3 treatment groups:
  - Group 1: tablet w/10 mg L + 2 mg Z
  - Group 2: gel cap w/350 mg DHA + 650 mg EPA
  - Group 3: both the tablet and gel cap

- On a daily basis

AREDS 2: Primary Study Outcome

- An additional 25% decrease in the risk of progression to advanced AMD in the three treatment groups over the study subjects taking the original AREDS1 supplement.

Study Subjects: AREDS 1 vs AREDS 2

- All stages of AMD
- Average age = 69
- 67% took Centrum (no L)
- Varied diets
- Varied serum L and Z
- More advanced stage
- Average age = 74
- 89% taking Centrum Silver (w/minimal L)
- Diet high in carotenoids and vegetables
- Higher serum L and Z

These differences could impact the ability to detect a more significant reduction in progression!

AREDS 2 First Results

"In the overall analysis, using 3 treatment groups, we found no significant difference in rates of macular degeneration," Dr. Chew said.
AREDS 2 Sub-group Analysis

- 10% reduction in progression to advanced AMD w/L&Z compared to no L&Z
- 18% reduction in progression in subjects who received L&Z + AREDS 1 supplement (without beta carotene) compared to those who took the original AREDS 1 supplement with beta carotene
- 26% reduction in progression in the participants taking L & Z that were in the lowest quintile of dietary L&Z intake

AREDS 2 Conclusions:
First, the Bad News

- Overall, the addition of 10 mg L and 2 mg Z, 1g DHA + EPA, or both to the AREDS formulation did not further reduce risk of progression to advanced AMD.

AREDS 2 Conclusions

- Results reaffirm previous epidemiological data showing that high dietary intakes of L&Z reduce the risk of AMD.
- Results support the safety and treatment benefits of substituting 10 mg L and 2 mg Z for beta carotene in AREDS formulations.
- Lower dosage of Zn was neither superior nor inferior, therefore I favor a 15-25 mg daily Zn dosage.

What about omega-3 EFAs?

- Fish oil supplement did not significantly alter the progression of AMD in AREDS 2.
- Perhaps the dosing was low, as at least 2g is used in CV studies.

AREDS 2 Limitations

- A greater reduction in AMD progression may have been demonstrated if the subjects’ diet had been more representative to that of the general US population.
- Inability to determine if the null findings are attributable to lack of efficacy of the supplements, inadequate dosing, inadequate Tx. duration, or a combination of these.

Macular Pigment Optical Density (MPOD)

Heterochromatic Flicker Photometry (HFP)
Risk assessment, early detection and monitoring of AMD

- Macular Pigment Optical Density (MPOD)

Xanthophylls and AMD

- Lutein and zeaxanthin form the macular pigment
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants and blue light screening compounds

The Importance of Macular Pigment

- Filters blue light
- Acts as an antioxidant by quenching free radicals
- Provides support to sensory retina

Test Results

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Questions, Comments, Stories?
“Superfoods”
AMD Prevention and Management

Dietary Sources of Lutein/Zeaxanthin

Dietary Lutein and Zeaxanthin: Eggs have high bioavailability

Lutein

Zeaxanthin
Dietary Zeaxanthin:
Gogi Berry

It would be naïve to assume that only 6 vitamins/nutrients are important in retinal health.

Essential Fatty Acids
(AMD, CVD, Stroke)

Dietary Vitamin D:
Cod Liver Oil, Sockeye Salmon

Modulation of cell growth
Neuromuscular and immune function
Reduction of inflammation

Blacks need 10 times more sun.

Cancer Belt:
Northern Latitudes
Breast, Prostate, Uterine, Colon

Loss of estrogen lowers vitamin D.

Osteoporosis
Winter Depression
(Seasonal Affective Disorder)

Low vitamin D
Hypertension
Autoimmune Disease
(Rheumatoid arthritis, Lupus)
Organ Transplant Rejection

Vitamin D Deficiency

Vitamin D Deficiency

For people aged one to 70 years, the RDA is at least 600 IU.
For people over 70, RDA is at least 800 IU.

Sunlight in a bottle
4000 IU Needed

90% Vitamin D from Sun Exposure

Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health

<12ng/mL, Deficiency leading to rickets in infants and children and osteomalacia in adults
12-20ng/mL, Inadequate for bone and overall health in healthy individuals
>20ng/mL, Adequate for bone and overall health
>50ng/mL, Potential adverse effects

Sources of Vitamin D

Table: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health

- Neo-bi fortified milk: 1 cup per day
- Fortified salmon, tuna, sardines, mackerel, herring: at least three servings per week
- "Sensible sunlight": Five to 15 minutes, two to five times per week
- Vitamin D3 supplements: 1,000 IU per day
Phototrop Study

- Improvement of Visual Function and Fundus Alterations in Early AMD Treated With a Combination of Acetyl-L-Carnitine, n-3 Fatty Acids, and CoQ10
- Feher, et.al.
- Ophthalmologica:2005;219:154-166
- 160 early AMD subjects randomized to Tx and controls
- 12 months
- VFMD, foveal sensitivity
- ETDRS VA, fundus exam
- All 4 parameters showed statistically significant improvement
- Principle: improved mitochondrial lipid metabolism

CoQ10

Not-so-guilty Pleasures

- Walnuts favorably affect cholesterol levels, reduce risk of heart disease.
- Dark chocolate, red wine are rich in antioxidants.
- Resveratrol enhances circulatory health (blood flow) and may have benefits in certain types of cancer.

Anti-oxidants, CA Fighters

- Walnuts favorably affect cholesterol levels, reduce risk of heart disease.
- Dark chocolate, red wine are rich in antioxidants.
- Resveratrol enhances circulatory health (blood flow) and may have benefits in certain types of cancer.

Folic Acid, B₆, B₁₂

- Folic Acid, Pyridoxine, and Cyanocobalamin Combination Treatment and Age-Related Macular Degeneration in Women: The Women's Antioxidant and Folic Acid Cardiovascular Study
- William G. Christen, ScD; Robert J. Glynn, ScD; Emily Y. Chew, MD; Christine M. Albert, MD; JoAnn E. Manson, MD

Folic Acid, B₆, B₁₂ in Foods
Folic Acid, B₆, B₁₂

5,442 female health care professionals 40 years or older with pre-existing CV disease

Randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo.

After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 \( P = .02 \)).

Pathways in AMD Pathogenesis

Questions and Comments?

Normal Retinal Metabolism

- Outer seg discs of rods and cones are transported to RPE for metabolism
- Discs are engulfed into RPE and fuse with lysosomes, where they are digested
- Undigested residual bodies remain as lipofuscin
- These are the real troublemakers!

Reactive Oxygen Species (ROS)

- ROS are the byproducts of oxygen metabolism:
  - free radicals
  - hydrogen peroxide
  - singlet oxygen

- The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen and its exposure to visible light.
The 4 Seasons of AMD
- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization

Vitreomacular Adhesion
- Accelerates the AMD process.
- Has a profound effect on NV in AMD.

Abnormal Retinal Metabolism
- Lipofuscin accumulates in the aging RPE

Pathobiology of AMD
- Aging of the photoreceptors and RPE
- Genetic component
- Environmental stress

Wet AMD Pathology

Pathogenesis of CNVM
- Breaks in Bruch’s Theory
- Diffuse thickening of Bruch’s w/soft drusen
- Predisposes Bruch’s to breaks
- New BV’s from CC grow and proliferate
Angiogenesis

Environmental factors
(hypoxia, pH)
Growth factors, hormones
(EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6, estrogen)

VEGF-A binding and activation of VEGF receptor

Endothelial cell activation

VEGF-A = vascular endothelial growth factor A; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; PDGF = platelet-derived growth factor; IGF = insulin-like growth factor; IL = interleukin.


Antiangiogenic Drugs: VEGF Inhibitors

VEGF binds to receptor
Anti VEGF Treatment

- Concept of antiangiogenesis was first proposed by Judah Folkman as a cancer treatment
- The concept has been extended to ocular proliferative retinopathies
- Three anti-VEGF treatments currently being used (Avastin, Lucentis, Eylea)

Case

- 81 Year old Female with a history of arthritis.
- 7 year history of injections with Avastin or Lucentis
- PMH: AMD OU, Cataracts OU
- OcHx: Injections for Wet AMD in OD

Ophthalmic Exam

- VA:
  - OD: 20/400  OS: 20/80
- IOP
  - OD: 11  OS: 12
- SLE:
  -OD: NS +1  OS: NS + 1
- DFE:
  -PED OD  and Geo Atrophy OS

OCT

After Switching to Eylea
QUESTION:
WHAT IS THE NEXT BREAKTHROUGH WET AMD TREATMENT?

ANSWER:

Fovista (Ophthotech)

- Phase 2 study
  - 24 week endpoint
  - Comparison of Fovista/Lucentis vs Lucentis monotherapy
    - 16.8 letters for combination therapy
    - 6.5 for Lucentis monotherapy
  - Development of subretinal fibrosis
    - 1% in combination group
    - 5% in Lucentis monotherapy group
- Phase 3 study underway
**Fovista (Ophthotech)**

- Anti-PDGF
- Platelet derived GF
- To be used with Anti-VEGF
- Decreases size of CNV when used w/Lucentis
- Better efficacy than Lucentis alone in Phase 2
- No adverse events at 6 mon
- Phase 3 under way w/Lucentis, Avastin, Eylea

**Squalamine lactate-** **Envlzon** (**Genera**)

Squalamine works INSIDE endothelial cells to block multiple intracellular pathways generated by the binding of VEGF and PDGFβ to receptors. TOPICAL DROPS.

**Is There a Strategy?**

- **USDA Food Triangle/My Plate**
- 5+ daily portions of fruits & veggies
- at least 1 dark green, leafy veg (spinach, kale)
- Low saturated/trans fat, low cholesterol
- Antioxidant for at risk patients
- L and Z
- CV Dx
- Physical Activity
- Low WL Blue, UV protection

**USDA Replaces Food Pyramid**

**Behavior Modification**

- Physical activity
- Fish consumption
- Greens
- Smaller portions
- Alcohol in moderation
- Nutritional supplements
- Blocking blue light from reaching retina
**Behavior Modification**
- Sedentary lifestyle
- Smoking
- Excess Alcohol
- High BMI
- HTN, Cholesterol
- Diet low in fish, green veggies

**Conclusions**
- AMD is on the rise.
- We must take proactive steps on behalf of our patients.

**Prevention**
- Early Diagnosis
- Early Intervention
- Improved Visual Outcomes

Thank you!

Joe

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