Imaging Dry AMD

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Financial Disclosure

**INDUSTRY**
Genentec-Roche (Site-PI on Lampalizumab Study GX29176)

**Government**
- NIH/NEI: RO1EY022097
- NIH/NIA: RO1 AG025392
- NIH/NEI: P30 EY006360
- NIH/NEI: R43 EY023504
- NIH/NEI: R43 EY016229

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- R. Howard Dobbs Jr. Foundation
- Minnesota Lions
- Emtech Biotechnology Grant
- The Fraser Parker Foundation
- Abraham J. and Phyllis Katz Foundation
- Research to Prevent Blindness
- Georgia Research Alliance

**Patents**
- Scleral Depressor: 8,083,751 B2 (US, 12-27-2011)
- Tissue Support Structure: 13/511,690 (US) #1 986 581 (Europe 10-3-2012)
- Postop Pain Formulation: 14011 Prov 09-27-2013
Bio-imaging of the Retinal Pigment Epithelium

Kabhilan Mohan
Department of Ophthalmology and Visual Sciences
University of Kentucky, Lexington, Kentucky
Prevalence

Dry AMD
Wet AMD

90%
10%

Liebowitz et al. Framingham Eye Study, 1980
CHAIRMAN'S MESSAGE
Best Ways to Prevent Aging?
Optimize
The diagram shows age distribution data for the years 2000 and 2010. Arrows indicate changes in the distribution from 2000 to 2010.

Sources: U.S. Census Bureau, Census 2000 Summary File 1 and 2010 Census Summary File 1.
United Nations

Individuals Over age 60
## Eye Disease Prevalence Research Group

*Arch Ophthalmol April ‘04*

<table>
<thead>
<tr>
<th>AMD</th>
<th>Citizens (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5% Prevalence</td>
<td>1.8</td>
</tr>
<tr>
<td>Year 2020</td>
<td>3</td>
</tr>
<tr>
<td>15% White Females &gt; 80</td>
<td></td>
</tr>
<tr>
<td>Drusen &gt; 125</td>
<td>7.0 at risk</td>
</tr>
</tbody>
</table>
Quality of Life

MODERATE AMD, Decrease in QOL is 32%

Severe Cardiac Angina or Hip Fx

Quality of Life

SEVERE AMD, Decrease in QOL is 60%

Advanced Prostate CA, Catastrophic Stoke

Bed Ridden, Incontinent, & Nursing Care

AMD IS COMMON
QOL is POOR
Lifestyle Risks
Leading Modifiable Risk Factor
Major Public Health Issue in China

Paul Hooson
Feb 2009
Permalink
Diet & Exercise... RISK?
Obesity and AMD?  
Especially for Men

OBESITY*

*An adult who has a body mass index of 30 or higher is considered obese.

Underweight <18  Normal = 18-25  Overweight = 25 to <30
Physical Inactivity + Diet Overload
Omega-3
AREDS REPORT # 30

1837 Patients

Highest Intake
30% less likely to develop
Advanced AMD (12 yr)

LUTEIN
AREDS REPORT # 22

4519 Subjects

Highest Intake had Lowest Risk of nAMD GA or Drusen

Vitamin D & AMD
Higher associated with Lower odds for AMD
1313 serum samples
Women

FITNESS & AMD

Lower Obesity
Higher Activity
Lowest Risk of AMD

FITNESS & AMD

BMES: >2000 x 15 yrs

After adjusting for other variables, Activity level was not Independently Associated w/ AMD

Encourage Risk Reduction
What is AMD?
Drusen
Drusen
Drusen
Drusen
Pseudodrusen Subtypes as Delineated by Multimodal Imaging of the Fundus

MIHOKO SUZUKI, TAKU SATO, AND RICHARD F. SPAIDE

Retrospective Observational

93 Subjects (selected cases)

3 Phenotypes:

Dot, Ribbon, “Peripheral”

Multi-modal Imaging is Important
Dot (96%): IR SLO
Ribbon (40%): Color Photo
Mid-Peripheral (9%)

+ 5 Yr
Drusen
Atypical Drusen
Genomic Data & AMD

CFH: 1q32, Tyr to His @ AA#402: Y402H

Klein et al. (15 authors) Science
   April 15, 2005 pp 385-9  Rockefeller U.  NY

Haines et al. (14 authors) Science
   April 15, 2005 pp 419-21  Vanderbilt University

Edwards et al. (6 authors) Science
   April 15, 2005 pp 421-4  Univ. Texas Southwestern

Zareparsi et al. (9 authors) Michigan
   Am J Hum Genet July 2005 pp149-53

Hageman et al. (27 authors) Proc Nat Acad Sci
   May 17, 2005 pp 7227-32  University of Iowa
## Asia vs Western

<table>
<thead>
<tr>
<th>Gene/Condition</th>
<th>Caucasian</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>++</td>
<td>- -</td>
</tr>
<tr>
<td>HTRA-1/ARMS-2</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Polypoidal</td>
<td>8-12%</td>
<td>25-50%</td>
</tr>
</tbody>
</table>

Image from Chan and Lai: HKJOphthalmol Vol 14 No 1
GENETIC VARIANTS

CFH Variant
BF & C2 (protective)
ARMS-2/HTRA-1

TLR3  Kleinman …Ambati; Nature 2008

SERPING-1  Enis …Lottery; Lancet 2008

Dicer, Alu RNA  Kaneko …Ambati; Nature March 2011

OTHER  \textit{COL8A1};\textit{FILIP1L}, \textit{IER3DDR1}, \textit{SLC16A8}, \textit{TGFBRI}, \textit{RAD51B}, \textit{ADAMTS9} and \textit{B3GALTL}; \textit{Nature Genetics, Fritche et al, 2013}
When do you use *commercial* genetic testing for assessing AMD risk?

- Never order
  - US 82.2%
  - Intl 93.2%
- Only in atypical AMD (younger, family history)
  - US 12.7%
  - Intl 4.5%
- Routinely order for patients with AMD
  - US 1.3%
  - Intl 1.1%
- Other
  - US 3.9%
  - Intl 1.1%
Assess Drusen
Communicate Risk
GA Progression Rate

181 of 4757 AREDS participants w/ GA
Progression rate: 2 mm² per year
Time to Center Involvement: 2-3 yrs
Va decreased 4 letters when center involved
Va decreased 4 lines @ 5 years

Lindblad et al. AREDS #26; Arch Ophthalmol 127;9;1168-74; 2009
AREDS 3
### AREDS #18

A Simplified Scale

<table>
<thead>
<tr>
<th>SCORE</th>
<th>5 YR RISK % progression to advanced Dz</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
</tbody>
</table>

Ferris et al, Arch Ophthalmol; 123;11, p1570-74; 2005
AREDS #18
Phenotype is Important
PREVENTION
An AREDS Update

Vitamin Supplementation and Progression of AMD

Numerous studies clearly link nutrition to the development and/or progression of age-related macular degeneration (AMD). This is not new information; for decades, eye experts have known of the connection between nutrition and AMD. So, in order to gain a better understanding of AMD and nutrition, the National Institutes of Health (NIH) and the National Eye Institute (NEI) cooperated to conduct the Age-Related Eye Disease Study (AREDS).

AREDS - Testing a Hypothesis

AREDS, which was completed in 2001, examined genetic and environmental factors affecting the natural progression of AMD and cataracts, and identified avenues of intervention. AREDS investigated the impact of zinc and antioxidants on AMD progression and identified subsets of patients most likely to benefit from nutritional supplements. The study found that the combination of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg zinc oxide), and copper (2 mg cupric oxide) reduced the risk of developing advanced AMD in about a quarter of high-risk study subjects.

AREDS data showed that high levels of antioxidants and zinc significantly reduced the risk of advanced AMD and its associated vision loss, and that these same nutrients had no significant effect on the development or progression of cataracts. High-risk patients could reduce by about 25% their risk of developing advanced AMD with high levels of antioxidants and zinc. Finally, while not a cure for AMD, supplements in the AREDS formulation may play a key role in helping people at high risk for developing advanced AMD maintain their remaining vision.

Based on the results from AREDS, it was recommended that patients over 55 years of age obtain dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen (between 63 and 125 microns, with 125 microns being the average width of a retinal vein where it crosses the optic disc); at least one large drusen, non-central geographic atrophy in one or both eyes or advanced AMD; or vision loss due to AMD in one eye, and who were non-smokers; were advised to consider oral supplementation with antioxidants plus zinc as used in the AREDS study.

Toward Further Answers - AREDS2

As with most good studies, AREDS answered important questions, but raised others. In AREDS, study subjects received 80 mg qd of zinc; high doses of zinc can cause prostate enlargement, and some evidence also suggests a link with Alzheimer’s disease. Studies have also pointed toward a link between beta-carotene supplementation and increased lung cancer risk in smokers.

In 2008, the NIH, again in cooperation with the NEI, launched the Age-Related Eye Disease Study 2 (AREDS2) to try to answer the questions that AREDS posed. The primary question became, then, could the same effects that were achieved in the AREDS study be duplicated with smaller dosages of zinc, and/or without the beta-carotene?

AREDS2 began following the full complement of recruited patients to determine if supplementation with xanthophylls (lutein/zeaxanthin) and/or omega-3 long-chain polyunsaturated fatty acids (LCPUFA - docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) could decrease progression to advanced AMD. The AREDS2 study uses xanthophylls: lutein 10 mg qd and zeaxanthin 2 mg qd, plus omega-3 long-chain PUFAs: DHA and EPA totaling 1 gm qd (AREDS2 primary formulation). The recruited patients receiving the primary formulation were further randomized to receive the AREDS-proven vitamin/mineral formulation with or without beta-carotene and a high/low dose of zinc.

AREDS2 Secondary Randomization Formulations

**FORMULATION 1**
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- Beta-Carotene, 15 mg
- Zinc Oxide, 80 mg
- Cupric Oxide, 2 mg

**FORMULATION 2**
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- Beta-carotene, 15 mg
- Zinc Oxide, 80 mg
- Cupric Oxide, 2 mg

**FORMULATION 3**
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- Zinc Oxide, 25 mg
- Cupric Oxide, 2 mg

**FORMULATION 4**
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- Zinc Oxide, 25 mg
- Cupric Oxide, 2 mg

AREDS 2 =
+ Lutein (10 mg)
+ Zeaxanthine (2 mg)
+ Omega-3 (DHA EPA 1 gm)
Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

The Age-Related Eye Disease Study 2 (AREDS2) Research Group*

AGE-RELATED MACULAR degeneration (AMD), the leading cause of blindness in the developed world, accounts for more than 50% of all blindness in the United States. In 2004, it was estimated that 8 million people 50 years of age and older in the United States had age-related macular degeneration (AMD). A study by the AREDS Research Group* showed that the AREDS formulation (antioxidant vitamins C and E, beta carotene, and zinc) was effective in reducing the risk of progression to advanced age-related macular degeneration (AMD).

Importance Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggest that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk.

Objectives To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation.
Advanced AMD & Lutein Zeaxanthine

LOWEST QUINTILE
Lutein/Zeaxanthin for the Treatment of Age-Related Cataract

AREDS2 Randomized Trial Report No. 4

The Age-Related Eye Disease Study 2 (AREDS2) Research Group*
Cataract & Lutein Zeaxanthine

LOWEST QUINTILE
Lutein Supplements in poorly nourished
The Intravitreal Injection
Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Study Group
MARINA STUDY

2 Year Phase III; NEJM: Oct 5, 2006; Rosenfeld, Brown, Heier, Boyer, Kaiser, Chung, Kim, & Marina Study Group
Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D., for the ANCHOR Study Group*
ANCHOR STUDY

2 Year Phase III; NEJM: Oct 5, 2006; Brown, Kaiser, Michels, Soubrane, Heier, Kim, Sy, Schneider, & Anchor Study Group
CATT STUDY: 1 yr Data

Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration.
Intravitreal Afibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

The Intravitreal Injection
What is your first-line anti-VEGF agent for wet AMD?

<table>
<thead>
<tr>
<th>Agent</th>
<th>US %</th>
<th>Intl %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>64.5</td>
<td>41.7</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>17.8</td>
<td>44.4</td>
</tr>
<tr>
<td>Aflibercept (Eylea)</td>
<td>16.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Pegaptanib (Macugen)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

PAT Survey ASRS 2014
What is your treatment strategy for wet AMD?

- See and treat patients monthly: US 2.0%, Intl 4.1%
- See patients monthly and treat only if there is activity: US 16.4%, Intl 37.2%
- Treat and extend: US 56.4%, Intl 77.9%
- Other: US 3.7%, Intl 2.3%
TREAT
No TREAT

Treat & Extend

PRN
What is your anti-VEGF therapy management choice for patients with bilateral wet AMD?

United States:
- 54.2% Inject both eyes at the same visit
- 41.9% Inject only 1 eye per visit
- 3.9% Other

International:
- 48.5% Inject both eyes at the same visit
- 47.7% Inject only 1 eye per visit
- 3.8% Other
Which anti-VEGF agent do you find most effective at decreasing fluid?

Eylea:
- US: 2.6%
- Intl: 4.9%
- Intl: 36.1%
- US: 48.4%

Avastin:
- US: 8.7%
- Intl: 14.3%

Lucentis:
- US: 40.3%
- Intl: 44.7%

All the anti-VEGF agents are equally effective at decreasing subretinal and intraretinal fluid.
PAT Survey ASRS 2014

Which anti-VEGF agent do you believe best treats the broadest range of wet-AMD patients?

- **Eylea**: US 57.8%, Intl 51.6%
- **Avastin**: US 6.6%, Intl 6.4%
- **Lucentis**: US 7.2%, Intl 9.0%
- **No difference**: US 28.4%, Intl 33.5%
Disciform scar
Va = 20/400
Continue to Tx?
Smaller scar
Va = 20/100
Continue to Tx?
Different configurations of outer retinal tubulation (ORT)

Summary

AMD is COMMON
QOL is POOR
AMD is not Caused by VEGF
AMD is not One Disease
Assess and Communicate Risk
“The Best Way to Predict the Future is to Create It.”

- Abraham Lincoln
Longer Term F/U
Horizon: Open Label Extension
Singer, Awh, Sadda, Freeman, Antoszyk, Wong, Tuomi

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

A Multicenter Cohort Study (SEVEN-UP)

hl-con-1?
Human Immune Conjugate Fusion Protein

mFVII  Hinge  IgG Fc Region
Anti-PDGF? + Anti-VEGF

Complement
Mullens et al, EYE 2001
Compliment Inhibition Lampalizumab?

MAHALO Study
Ab Binds Factor D
Reduced GA progress
Complement factor I Biomarker
Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt’s macular dystrophy: follow-up of two open-label phase 1/2 studies

Steven D Schwartz, Carl D Regillo, Byron LLam, Dean Elliott, Philip J Rosenfeld, Ninel Z Gregori, Jean-Pierre Hubschman, Janet L Davis, Gad Heilwell, Marc Spinn, Joseph Maguire, Roger Gay, Jane Bateman, Rosaleen M Ostrick, Debra Morris, Matthew Vincent, Eddy Anglade, Lucian V Del Priore, Robert Lanza

www.thelancet.com online October 15, 2014
Dry AMD
IMT
Implantable Miniaturized Telescope

www.google.com/
Extra-Ocular Telescope: Bioptic

Model Image Release Signed for Public Presentations or Publication
Thank You!