AMD Update

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Mark Dunbar: Disclosure

- Consultant for Allergan
- Optometry Advisory Board for:
  - Allergan
  - Carl Zeiss Meditec
  - Artic Dx
  - Alcon Nutrition
  - Sucampo
- Speakers Bureau
  - Allergan
  - Carl Zeiss
  - Artic Dx

Mark Dunbar does not own stock in any of the above companies

Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2° to CNV
  - Develops in 1.2% of adults 43-86 yo (Wisconsin Beaver Dam Eye Study)

ARMD

- Patients Affected
  - 10% wet or exudative
  - 90% dry or nonexudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry

Dry ARMD

- Earliest clinically detectable feature
- Lie between BM of RPE and Bruch’s
- Hard drusen: smaller, calcified or ossified
- Soft drusen: ill-defined, larger, coalesce, resemble small serous detachments

AREDS Staging

Category 1
- No or few drusen (< 63 microns), no pigment abnormalities, neither eye Wet
- 0% risk of Wet at 5 yrs

Category 2
- Intermediate drusen (< 125 microns), mild pigment abnormalities, neither eye Wet
- < 2% risk of Wet at 5 yrs

Note: Central retinal vein is approximately 125 microns
AREDS Staging

Category 3/Intermediate
- Combo of extensive intermediate or any large drusen, or GA
- 18% risk of Wet in 5 yrs

Category 4/Advanced/High Risk
- One eye with Wet or BCVA worse than 20/32 from Dry
- >42% risk of Wet in 5 yrs

Risk of Progression to Wet AMD
- Strongly dependent on age and stage of the dry AMD
  - Soft drusen
  - RPE pigmentation

Progression of AMD
- < 60 y/o with a normal macula: 5 yrs risk of developing retinal changes or early maculopathy = 0.7%
- 80 y/o with normal retina and no drusen:
  - 5 yr risk of retinal changes or early maculopathy = 22.5%
- 80 y/o with Soft Drusen and RPE Changes:
  - 5 Yr risk of progression to Wet AMD = 42%

CNV
- Clinical Sign of CNV
  - Subretinal fluid
  - Subretinal hemorrhage
  - Exudate
  - Gray-green pattern of pigment

Choroidal Neovascular Membranes (CNV)
- Invade Bruch’s membrane
- Perforate intact Bruch’s membrane
- Grow through defects in Bruch’s

CNV
- Significant cause of vision loss in both the working class and geriatric population
- Mechanism is not completely understood
  - Any pathologic process that involves RPE and damages Bruch’s membrane can be complicated by CNV
  - What is the stimulus that causes the growth of CNV?
### AMD: Established Therapies

- **Thermal laser photocoagulation**
- **Photodynamic therapy with Visudyne™**
  - FDA approved for:
    - Subfoveal predominantly classic lesions
    - Subfoveal minimally Classic or Occult-only – but Lesions must be < 4DD in size – or must be demonstrated disease progression
- **Anti-VEGF Therapy**

### Vascular Endothelial Growth Factor (VEGF)

- **Multifunctional protein**
- **Mediator of developmental and pathological vascularization**
- **Angiogenic and vascular permeability properties**

### VEGF

- **VEGF165 is selectively increased during pathological neovascularization**
- **Blocking VEGF165 inhibits pathological neovascularization; spares normal vessels**

### Anti-VEGF Therapy

- **Represents 1st validated biologic switch in the treatment of pathologic CNV**
- **Major paradigm shift in how we treat neovascular and hyperpermeability diseases**
- **Targeting the root cause of CNV**

### Lucentis (Genentech)

- **Recombinant humanized antibody “fragment” binds to VEGF**
  - Targets a different isoform of VEGF than Macugen
- **Prevents VEGF from interacting with the VEGF receptor on the surface of endothelial cell**
- **Injected into vitreous**
- **Transparent jelly-like substance fills the vitreous cavity**
  - Rapidly passes through the retina and into the subretinal space to the RPE (1hr)

### Ranibizumab for Neovascular Age-Related Macular Degeneration

*Philip J. Rosenfeld, M.D., Ph.D., et al., for the MARINA Study Group*

*NEnglJMed 2006;355:1419-1431*
**Lucentis Phase III Clinical Trials**

- **MARINA trial**
  - AMD pts with subfoveal minimally classic or occult-only CNV tx with monthly injections 300g or 500g vs. sham
  - Followed for 24 months

- **ANCHOR trial**
  - Predominantly classic CNV to receive monthly injections of 300g or 500g vs. PDT
  - Evaluated q 3 mo then receive PDT vs. placebo
  - 1° endpoint is lose of at least 15 letters of VA
  
**Principal Eligibility Criteria**

- Age ≥50 years
- VA (Snellen equivalent) 20/40 to 20/320
- Subfoveal CNV secondary to AMD
- No prior PDT
- Lesion composition by fluorescein angiography
  - Area of CNV must be ≥50% of total lesion
  - Minimally classic or occult with no classic
  - Evidence of presumed recent disease progression
  - Blood, recent growth by FA, or recent VA loss
- Lesion size ≤12 disc areas (DA)

**Secondary Endpoint: Mean Change in Visual Acuity Over Time**

**Conclusions: 2-Year Results**

- Ranibizumab demonstrated a clinically and statistically significant benefit over sham through 24 months of treatment
  - ≥90% of subjects lost <15 letters
  - 5.4- to 6.6-letter improvement in mean VA compared to baseline
  - ~20-letter benefit compared to sham
  - 26% to 33% improved ≥15 letters
  - 5% to 5.8% improved ≥30 letters
  - Other visual and anatomical outcomes favored ranibizumab

**Principal Eligibility Criteria**

- Age ≥50 years
- VA (Snellen equivalent) 20/40 to 20/320
- Primary or recurrent subfoveal CNV lesion secondary to AMD
- No prior PDT
- Lesion composition by fluorescein angiography
  - Classic CNV ≥50% of the total lesion area (predominantly classic lesion)
  - Total lesion ≤5400 µm in greatest linear dimension
Secondary Endpoint: Mean Change in Visual Acuity Over Time

Conclusions
- Ranibizumab treatment resulted in a clinically and statistically significant benefit compared to PDT in predominantly classic CNV after 12 months of treatment.
  - ~95% of subjects lost fewer than 15 letters
  - 8.5- to 11.3-letter improvement in mean VA compared to baseline
  - 36%-40% gained ≥15 letters
  - 6%-12% gained ≥30 letters
  - Other visual and anatomic outcomes favored ranibizumab

Lucentis Phase III Results: MARINA and ANCHOR Trial
- 95% treated eyes maintained vs. 60% control group at 12 and 24 months
- 40% of treated patient had 20/40 VA vs. improvement in VA
- 90% treated with Lucentis at year two maintained or improved vision compared to 53% in the control arm

Conclusions
- Ocular serious adverse events occurred in <0.1% of intravitreal injections
- No imbalance in nonocular adverse events overall

Avastin® (bevacizumab, Genentech Inc.)
- First anti-VEGF therapy approved by the FDA
- Avastin® Bevacizumab MW 150 kD

Why consider Avastin in ophthalmology?
- Patients losing vision on current therapies
- Lucentis and Avastin have nearly identical binding properties
  - Functionally the same molecule
- Avastin is available off-label
- Intravitreal Lucentis improves vision but not yet FDA approved
Intravitreal Avastin for Neovascular AMD

- First patient treated in May, 2005
- Case reports published in July, 2005
- Global clinical use in less than 6 months
- Medicare coverage in a majority of states

Lucentis vs. Avastin (Genentech vs Genentech)

COST

- Lucentis -> $2500 - $3,000 per injection
  - $3300 per mg
- Avastin -> $5.50
  - 1.25 mg costs $6.88
- If dispensed by a licensed pharmacist directly from the vial to the syringe, cost rises to between $17 and $50 a syringe

Economic Analysis

Total 2 year cost for AMD treatments

- Avastin: $2,037
- Visudyne/PDT: $11,162
- Macugen: $27,276
- Lucentis: $67,128

Intravitreal Avastin

- Appears non-toxic in cell culture and animal studies
- Appears safe and effective in short-term retrospective and prospective studies
  - Highly reproducible!
- Optimal dose and dosing interval is unknown

Avastin vs. Lucentis

What is the Treatment of Choice?

- NEI/NIH to sponsor head-to-head trial
- Complications of Age-Related Macular Degeneration Treatment Trial (CATT)
- 1200 patients randomized
  - Lucentis with 4 week dosing
  - Avastin with 4 week dosing
  - Lucentis with variable dosing
  - Avastin with variable dosing
- Followed for 2 yrs, and 4 yrs to complete

Highlights

- 1208 Pts Randomized
- Equivalent VA outcomes: Ranizumab vs. Bevacizumab
  - Lucentis gained 8.5 letters vs. Avastin 8 letters
- Equivalent VA outcomes: monthly vs. PRN ranibizumab
- Inconclusive/ significant difference in VA Bevacizumab monthly vs PRN

4/28/2011, NEJM.org
Avastin vs. Lucentis
What is the Treatment of Choice?

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  - Lucentis with variable dosing
  - Avastin with variable dosing
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Statistics From CATT 1 Year Results

<table>
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<th>Lucentis Monthly</th>
<th>Lucentis PRN</th>
<th>Avastin Monthly</th>
<th>Avastin PRN</th>
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<tr>
<td>Average change in acuity (letters gained)</td>
<td>8.5</td>
<td>6.8</td>
<td>8.0</td>
<td>5.9</td>
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<tr>
<td>Average ending visual acuity score (mean no. of letters)</td>
<td>68.8</td>
<td>68.4</td>
<td>68.4</td>
<td>66.5</td>
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<tr>
<td>Decrease in CMT (μm)</td>
<td>196</td>
<td>168</td>
<td>164</td>
<td>152</td>
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<tr>
<td>Number treatments needed</td>
<td>11.7</td>
<td>6.9</td>
<td>11.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Systemic adverse events (TIA, MI, CVA, HTN)</td>
<td>6.9%</td>
<td>7.3%</td>
<td>8.0%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

Economic Analysis

Total 2 year cost for AMD treatments
- Avastin: $2,037
- Visudyne/PDT: $11,162
- Macugen: $27,276
- Lucentis: $67,128

Lucentis vs. Avastin

- Large prospective comparative clinical trials comparing ranibizumab with bevacizumab will begin in 2007:
  - (US/NEI) Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Daniel Martin, MD
  - (UK/NHS R&D) A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) Trial Usha Chakravarthy, MD

FDA Warns of Problems with Bevacizumab (Avastin)

- FDA today warns that intravitreal injections of repackaged bevacizumab (Avastin) has caused a cluster of serious Streptococcus endophthalmitis infections and blindness in Miami, FL
- 12 cases of endophthalmitis resulting from a pharmacy in Hollywood, Florida, that repackaged Avastin from sterile, injectable, single-use preservative-free vials into individual 1-mL single-use syringes
**Eylea**

- VEGF Trap-Eye
- Mimics the VEGF receptor, traps VEGF
- Recently FDA approved for q8wk dosing
- Q8wk dosing = q4wk Lucentis dosing

**Eylea: VEGF Trap by Regeneron**

- Recombinant soluble VEGF receptor with affinity to all VEGF-A, placental growth factor 1&2, VEGF-B,C&D
  - Creates decoy receptor to "Trap" the VEGF
- VEGF Trap-EYE
  - Intravitreal injections
  - Similar ophthalmic results without systemic findings

**Lampalizumab (LAMP) Anti-factor D (Genentech)**

- A monoclonal antibody that inhibits Complement Factor D
  - A rate-limiting enzyme involved in the alternative complement pathway
  - A “key-driver” for the development of geographic atrophy

**MAHALO Trial**

- 129 pts with bilateral geographic atrophy randomized to assess the safety, tolerability, and activity of lampalizumab (LAMP)
- Biomarkers for complement factor H (CFH), C3, C2/CFB and CFI were also determined
- Participants, 60 - 89 y/o randomized to lampalizumab 10 mg or sham injections
MAHALO Trial

- A positive treatment effect was seen in the monthly lampalizumab group beginning at month 6, and was maintained through month 18 with primary and secondary imaging end points.
- Subgroup analysis of monthly injections showed overall reduction in GA area in pts with a specific biomarkers was more than double that of the study cohort as a whole (44.0% vs. 20.4%).

Geographic Atrophy and Complement Factor I (CFI)

- 57% of genotype samples collected from 93 patients were positive for the CFI biomarker.
- CFI biomarker is both prognostic for GA area progression and predictive for lampalizumab treatment response.

Can We Inhibit the Process of “Compliment Activation?”

- Analysis of drusen in pts with AMD show high levels of some end products of complement cascade (factors C3 and C5).
  - Factor C3a and C5a found in drusen in patients with wet AMD.
  - C3a and C5a induce VEGF production in vitro and in vivo.

The Role of Diet and Nutritional Supplements

Lifestyle Changes to Prevent AMD

- Does making lifestyle changes prevent the development.
- Justifiable in other diseases.
  - Diabetes, hypertension and heart disease.
- Can it affect the development of AMD?
- What is the role of nutrition in AMD?
  - What about antioxidants and other vitamins and supplements on AMD?

Age Related Eye Disease Study (AREDS)

- Purpose: Assess clinical course, prognosis, and risk factors of ARMD and Cataract.
- To evaluate (randomized clinical trial) the effects of pharmacologic doses of:
  - Antioxidents and Zinc on the progression of ARMD.
  - Antioxidents on the development and progression of lens opacities.
AREDS

- 11 Center double-masked controlled clinical trial
- Recruitment began Nov 1992, ended Jan 98
- 90% followed for a minimum of 5 years
- 3640 people enrolled and categorized

- Extensive small drusen
- Intermediate drusen
- Large drusen
- Noncentral geographic atrophy
- Pigment epithelial abnormalities
- Advanced AMD or vision loss in 1 eye

AREDS

4757 Pts (55-80 yrs of Age) from 11 Centers Randomized 3640 Studied

- 1117 excluded because no AMD
- Zinc alone
- Antioxidants alone
- Combination of antioxidants and zinc
- Placebo

The Nutrients

- Vit C 500 mg
- Vit E 400 international units
- Beta-carotene 15 mg
- Zinc 80 mg (Zinc oxide)

- 2/3 chose to take an additional multi-vit

AREDS Results

Arch of Ophthalmol Oct 2001

- 592 Developed CNV, 257 developed geographic atrophy
- Group 1: Early AMD (1063 Pts)
  - Only 15 progressed over 5 yrs VA loss due to CNV or geographic atrophy: 1.3% probability
  - Projected 50
- 316 progressed to group 2 and 3
- Group 2 and group 3: 834 total

AREDS Results

Arch of Ophthalmol Oct 2001

- “Eyes at high risk of developing Advanced AMD lowered their risk by 25% when treated with high dose combination Vit C, Vit E, beta-carotene and zinc”

AREDS Results

Arch of Ophthalmol Oct 2001

- AREDS was unable to determine potential treatment benefits among early AMD pts
  - Slow progressive trend
  - Not likely to progress to an advance stage of AMD
  - These groups make up a large number of our pts
  - Oral supplements did not have any effects on cataract progression
**AREDS Results**
Arch of Ophthalmol Oct 2001

- Those with intermediate and advanced AMD benefited from taking antioxidants and zinc
- For those study participants who had either no AMD or early AMD, the supplements did not provide an apparent benefit

**AREDS Results**

- Nutrients are the 1st effective Tx to slow the progression of AMD

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**AREDS 10 Yr Follow Up**

- For patients with no large drusen in either eye at baseline: the rate of advanced AMD at 10 years is 1.1%
- Patients with large drusen or pigmentary changes in one eye or both eyes: rate of CNV is 72% at 10 years
- AREDS formulation resulted in 27% reduction in the risk of progression to advanced AMD

**AAO 2008**

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**Age-Related Eye Disease Study 2**

- Multi-center, randomized trial designed to assess the effects of
  - Oral supplementation of macular xanthophylls (lutein and zeaxanthin) and/or
  - Long-chain omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA])
- On the progression to advanced AMD

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**Age-Related Eye Disease Study 2**

- Assess whether forms of the AREDS nutritional supplement with reduced zinc and/or no beta-carotene works as well as the original supplement in reducing the risk of progression to advanced AMD

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**Age-Related Eye Disease Study 2**

- 4,000 pts ages 50 to 85 who are at high risk of having advanced age-related macular degeneration randomized
- Pts will be randomized to: placebos (sugar pills) vs. standard AREDS formulation
  - (Vit C, Vit E, beta-carotene, zinc oxide, and copper)
  - Pts who have smoked within the past year will not receive the standard formulation b/c beta-carotene
AREDS 2: Primary Analysis

- Does adding lutein and zeaxanthin, DHA + EPA, or a combination of the two to the AREDS formulation reduced the risk of progression to advanced AMD by an additional 25% as compared to study subjects taking the original AREDS supplement?
  - Which was the study control arm

AREDS 2

- The Answer:
  - The data did not demonstrate a significant reduction in progression to advanced AMD in any of the three treatment arms as compared to the control group.
  - So...
  - AREDS 1 supplement just as good as AREDS 2
  - But...

Secondary Analysis

- 10% reduction in progression to advanced AMD when compared to no lutein + zeaxanthin
  - That does not mean 10% + the original 25%

- 18% reduction in progression to advanced AMD in subjects who received the AREDS supplement with L/Z in place of beta carotene compared to the original AREDS

- 26% reduction in progression to advanced AMD in the lowest quintile of dietary lutein and zeaxanthin intake

Conclusions

Comparisons of the three active arms to control (primary analyses) did not significantly reduce risk of progression to AAMD.

The addition of lutein/zeaxanthin to the AREDS formulation as analyzed by the main effect showed 10% decrease in risk of progression to AAMD.

No main effect efficacy with DHA/EPA.
Conclusions

Secondary randomization suggests no differences in the progression to AAMD for elimination of beta-carotene or lowering zinc dose

No differences in adverse side-effects (gastrointestinal disorders or others) between “low” and high zinc groups

Insufficient data to make recommendation for zinc

Conclusions

The main effect of lutein/zeaxanthin demonstrated 10% reduction of AAMD

~ 20% reduction in the risk of progression to AAMD of L/Z beyond the effects of AREDS supplement in persons with the lowest dietary intake of L/Z

~ 20% reduction in the risk of progression to AAMD, particularly neovascular AMD, of L/Z in head-to-head comparison with beta-carotene

Conclusions

Improve the safety of the AREDS supplements by removing beta-carotene to decrease the risk of lung cancer in smokers and former smokers who compose >50% of persons with AMD.

Conclusions

Considering the totality of evidence, lutein/zeaxanthin may be an appropriate carotenoid substitution for beta-carotene in the AREDS formulation

AREDS2 Formulation

Vitamin C (500 mg)
Vitamin E (400 IU)
Beta Carotene (15 mg)
Lutein (10 mg)/Zeaxanthin (2 mg)
Zinc (80 mg zinc oxide)
Copper (2 mg cupric oxide)
Omega-3 fatty acids (DHA/EPA)

Understanding the Disease… Finally
NEI News Release
March 2005
Gene Found to Increase Risk of AMD

- 4 independent research teams (including NEI) discovered a gene that is "strongly associated" with the development of AMD
- Gene is called Compliment Factor H
- CFH gene produces a protein that helps regulate inflammation in part of the immune system that attacks diseased and damaged cells
- Those whose genetic makeup includes a variant of the CFH gene are 7.4 X more likely to develop AMD

The Compliment System

- Complement activation is an inflammatory process involving dozens of plasma proteins, ultimately leading to cell membrane disruption through the membrane attack complex (MAC)
- Activation of the complement system is an important part of the body's defensive immune response against pathogens such as bacteria and viruses
- Inappropriate or excessive complement activation can have destructive consequences

The Compliment System

- The Complement Pathway is one of the body's primitive defense systems - more primitive than antibodies, that fights against disease
- Complement activation is an inflammatory process involving dozens of plasma proteins, ultimately leading to cell membrane disruption through a process called the membrane attack complex (MAC)
- Inappropriate or excessive complement activation can have destructive consequences

Understanding AMD: Putting it All Together

- CFH helps regulates this complement system to prevent it from "getting out of control"
- Drusen contain most all of the proteins that make up the complement system
- AMD may result from a deficiency in regulation of the Complement System
  - Key driver in angiogenesis

Age-Related Macular Degeneration (AMD)
2005 - 2008: Three complement genes strongly associated with AMD

- 2005: Complement Factor H (CFH)
- 2006: Component C2/Factor B
- 2007: Component C3
- Component C7
- Mannose Binding Lectin 2
- 2008: CFH-related gene 1 (CFHR 1)
- CFH-related gene 3 (CFHR 3)
- C1 Inhibitor

Compliment Activation

- "Two-hit theory"—defect in CFH locus not enough to cause AMD
- Smoking/infection, and other mediating factors thought involved in development of AMD
Risk Factors: Smoking

- Smoking is #2 risk factor to age
- Smoker: 2.4x
- Smoker and CFH: 34x
- Need awareness

Revolutionary Genetic Test Now Available for AMD

- March 10, 2009: For the first time ever, an individual’s inherent risk of developing this devastating eye disease can be determined
- ArcticDX inc: a molecular diagnostic company with expertise in the design, development and commercialization of validated molecular diagnostic tests
- The test is called: Macula Risk (R)

AMD – A Genetic Disease

Macula Risk®
A test that identifies AMD patients that will progress to Adv stage of dz with associated VL.
83% Predictive Value*

The Genetic Components of AMD

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<th>Marker</th>
<th>Allele</th>
<th>Odds Ratio</th>
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<td>CFH</td>
<td>H1+H3 (risk)</td>
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<td>Average</td>
<td>&gt;17</td>
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<td>(H2+H4)</td>
<td>&gt;17</td>
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<tr>
<td>C3</td>
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The Genetic Components of AMD

3 Gene Groups Involved in AMD

- Inflammation
- Oxidation
- Mitochondrial health

Macula Risk® Score
Risk of Progressing to Advanced AMD by 80 Years of Age

The Macula Risk® results place the patient in 1 of 5 different categories which correlates to the patient’s risk of developing AMD that progresses to vision loss.
RetnaGene

NEW COMMERCIAL MODEL

Old Model
- Reimbursed: Medicare & Third-Party Payors
  - SQNM bills payors (95% Medicare)*
  - Minimal/no cost to patient
  - Patient Assistance Program
  - 9 field reps
  - 1st position, focus on Retina

New Model
- Patient-pay: Medicare-decision of non-coverage in Jan 2014
  - Client-billing w/ patient mark-ups allowed (per state laws)
  - Direct-to-patient billing (NY, NJ, RI)
  - 30+ field reps
  - 2nd position, focus on General Ophthalmology, Optometry

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

- Genetic analysis of 995 patients with intermediate (moderate) AMD who were in the original AREDS 1 study
- Followed for 12 years
- Evaluated the interaction of genetics and type of nutritional supplement on progression from moderate to advanced AMD

Genetic Testing and Recommending Nutritional Supplements

- Of the estimated 15 million Americans taking the AREDS formula, more than ten million should not be on either zinc or antioxidants
- Only about 23% of patients taking AREDS formula should be while the vast majority should not
- Genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared to treatment with the AREDS formulation

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

- Patients with genetically determined CFH high risk alleles, zinc was associated with increased progression to advanced AMD
- Patients with ARMS2 high risk alleles, treatment with antioxidants worsened the outcome
- The researchers demonstrated that patients with CFH risk alleles benefit from antioxidants without zinc but patients with ARMS2 risk alleles benefit from zinc without antioxidant
More than double the benefit of AREDS:

“We estimate that genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared with treatment with the AREDS formulation.”

A clear role for genetic testing – Ivana Kim (co-author)

“This data demonstrates that the composition of supplements recommended to AMD patients should be guided by an individual’s genetic risk profile, indicating a clear role for genetic testing in clinical management.”

**What is the Relationship between Genetics, AMD and AREDS Supplement?**

- Patients with genetically determined CFH high risk alleles, zinc was associated with increased progression to advanced AMD
- Patients with ARMS2 high risk alleles, zinc was associated with **DECREASED** progression to advanced AMD antioxidants worsened the outcome
- Patients with CFH risk alleles benefit from antioxidants **without zinc** but patients with ARMS2 risk alleles benefit from zinc **without antioxidant**

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

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- Followed for 12 years
- Evaluated the interaction of genetics and type of nutritional supplement on progression from moderate to advanced AMD

49% derive more benefit from treatment other than AREDS

**Estimate Probability of Progression**

*Figure modified from Ivan et al.*, CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology 2013.
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A clear role for genetic testing – Ivana Kim (co-author)

This data demonstrates that the composition of supplements recommended to AMD patients should be guided by an individual’s genetic risk profile, indicating a clear role for genetic testing in clinical management.”
Conclusions
The AREDS supplements reduced the rate of AWD progression across all genotype groups. Furthermore, the genotypes at the CFH and ARMS2 loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD.

Wait - But that’s Not All...

Treatment Responses to Antioxidants and Zinc based on Genetic Profiles

Conclusions: The benefit of the AREDS formulation seems the result of a favorable response by patients in only 1 genotype group, balanced by neutral or unfavorable responses in 3 genotype groups.
Genetic Testing and Recommending Nutritional Supplements

- Of the estimated 15 million Americans taking the AREDS formula, more than ten million should not be on either zinc or antioxidants
- Only about 23% of patients taking AREDS formula should be while the vast majority should not
- Genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared to treatment with the AREDS formulation

Can We Inhibit the Process of “Compliment Activation?”

- Analysis of drusen in pts with AMD show high levels of some end products of complement cascade (factors C3 and C5)
  - Factor C3a and C5a found in drusen in patients with wet AMD
  - C3a and C5a induce VEGF production in vitro and in vivo

Compliment Activation

- C3 is the central component of all major complement activation pathways
- Inhibition of C3 effectively shuts down the downstream complement activation pathway
Pathways for Complement Activation

- All pathways lead to C3 and C5 activation
- Terminal complement activation results in Membrane Attack Complex (MAC)
- Are complement proteins in the retina and choroid?

C5 Inhibition Blocks Terminal Complement Activation

- SOLIRIS and ARC 1905 bind with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact
- C3a anaphylatoxin produced
- Immune complex and apoptotic body clearance
- Microbial opsonization

Making Sense of it All

Sources of L/Z

- ~78% of dietary L and Z is sourced from vegetables
  - L is found in highest concentrations in dark green leafy vegetables: spinach, kale and collard greens
  - Z is found in corn, orange peppers and oranges, with a high mole percentage of both L and Z being found in egg yolk
- Possible dietary sources of meso-Z include shrimp, certain marine fish and turtles

LUTEIN

- From Food
  - Spinach
  - Broccoli
  - Corn
  - Orange peppers
  - Kiwi
  - Grapes
  - Egg yolk
- From Marigolds

ZEAXANTHIN

- Red pepper, paprika a major source for supplements
- Found in foods
- 1 cup diced red pepper = 1mg Zeaxanthin
An average western diet contains 1.3–3 mg/day of L and Z combined with significantly more L than Z (7:1).

### Summary

- Anti-Angiogenic therapy appear to be the future for the treatment of CNV and retinal vascular disease
- Represent a major shift in the paradigm of Tx for CNV
- Lucentis and Avastin have shown remarkable results beyond what has been seen previously