Disclosures

• No pertinent financial disclosures

• I will discuss the use of off label bevacizumab for use in wet AMD.
Dry and Wet AMD

- Dry AMD & Wet AMD
- What is it?
- How do we treat it?
- What’s coming?
1900 = 47 years

2013  66%  79 years

AMD Prevalence 35% > Age 75

From C.C.W. Kliuver, 2009
Who gets AMD?

Fair skinned populations of European decent have the highest rates of AMD

> 50%
Genetic

Black Death

1347-1351 → 50% died

Complement Mutations

Increase ability to fight *Yersinia*

Survival benefit → selection pressure

Complement Factor H Variant Increases the Risk of Age-Related Macular Degeneration
Causes of Blindness

- Cataract
- Glaucoma
- AMD
- Diabetic Retinopathy
- Other

Aspirin = Acetylsalicylic acid
- Anti-pyretic
- Anti-inflammatory
- Anti-platelet

40,000 Tons
Isolated in 1897
Hippocrates 400BC

Interventional Studies

- Women's Health Study >39,000
  - 100mg QOD → 10-18%
- Physician's Health Study >21,000
  - 325mg QOD → 22%

Insignificant protective effect of aspirin on advanced AMD & vision loss
Supplements

Supplements

• $30,000,000,000 industry
• MVI, minerals or herbs
• 42% in 1988
• 58% in 2012
• Eye health supplements are one of the strongest growth sectors
  • Increased 9% in 2012 ($114 million)

Dietary supplements = not regulated by the FDA in the same way as pharmaceuticals
Makers do not have to prove safety or efficacy

Age-Related Eye Disease Studies

NIH / NEI Sponsored
AREDS-1

Randomized Participants 4,757

Placebo 1,483 Antioxidant 1,482 Zinc 904 Antioxidant + Zinc 888

Dry AMD – Drusen Photos

Drusen

Confluent Drusen

Drusen Diameter (µM)
Small < 62
Intermediate 64-124
Large > 124

Intermediate AMD =

Extensive intermediate or any large drusen
Drusen

Metabolic waste & inflammatory debris below RPE within Bruch’s membrane
Progression to Advanced AMD

- Placebo: 44%
- Antioxidants: 34%
- Zinc: 30%
- Antioxidants + Zinc: 20%
- 0%

P vs. A+Z – p<0.01

27% Risk Reduction

5 Year Risk of Advanced AMD

- 1 point each eye
- Drusen
- Pigment abnormalities
- 2 points if neovascular AMD

Age-Related Eye Disease Study (AREDS) - 2

- New supplements
  - Carotenoids (Xanthophylls)
    - Lutein/Zeaxanthin (L/Z) – 10mg/2mg
  - Omega-3 Long Chain Polyunsaturated Fats
    - Docosahexaenoic Acid (DHA) – 350mg
    - Eicosapentaenoic Acid (EPA) – 650mg
  - Optimizing original AREDS-1 formulation
Large drusen OU (65%) GA Wet AMD

All Eyes = High Risk of Progression to Advanced AMD

Primary Randomization

Participants
4,203

Control
Lutein/Zeaxanthin
DHA/EPA
L/Z + DHA/EPA

All with AREDS-1 Supplements

Progression to Advanced AMD

Control (AREDS-1)
L/Z
DHA/EPA
L/Z & DHA/EPA

Years
0 1 2 3 4 5

% Progression
0% 10% 20% 30% 40%
10% risk reduction with L/Z
HR=0.90  P=0.04

Progression by Dietary Intake of Lutein & Zeaxanthin

26% reduced risk (p<0.01)

18% risk reduction with L/Z vs BC
HR=0.82  P=0.02

Progression to Advanced AMD
Smoking, Beta-carotene & Lung Cancer

- In smokers, beta-carotene can increase lung cancer risk
- AREDS-2: assigned to no beta-carotene
  - All current smokers
  - Smoked w/in 1 year
- Analysis: nonsmokers & those who stopped >1 year

- Beta-carotene 2% (n=23)
- No Beta-carotene 0.9% (n=11)
- 91% (n=31) were former smokers who quit >1 year

AREDS-2

- Vitamin C 500 mg
- Vitamin E 400 IU
- Zinc 80 mg
- Copper 2 mg
- Lutein 10 mg
- Zeaxanthin 2 mg

I'm taking a general multivitamin, that's enough right?
- No, AREDS + general multivitamins
- 66-89% of AREDS patients took MVI

Can I get the nutrients from my diet & not take supplements?
- No. Doses are too high (US diet: 1-2 mg/day L+Z)
I don’t have AMD but my mom does. Can I take AREDS vitamins to prevent AMD?  
*Don’t know! No proven benefit in primary prevention*

I have advanced AMD in both eyes. I don’t need to take AREDS, right?  
AREDS recommended if VA ≥ 20/100

I smoke. What AREDS formula do I take?  
Everyone takes the same formula (no beta-carotene)

**Side Effects?**
- Lutein & Zeaxanthin: None  
- Vitamin C  
  - Kidney stones (>1000mg)  
  - In DM → ↑ Increased BS  
- Vitamin E  
  - Prostate Cancer  
- Zinc  
  - BPH  
  - Prostate Cancer  
  - UTIs  
- Copper: taken to prevent zinc associated anemia  
  - Kidney dysfunction (>10mg)

**“Is It lucky to have Dry AMD?”**
- While exudative AMD accounts for majority of legal blindness, patients with dry AMD often symptomatic  
  - Suffer similar to wet AMD patients  
    - Depression  
    - Reading difficulty  
    - Contrast sensitivity loss
**Geographic Atrophy**

- Severe form of dry AMD
- Loss of RPE
- Leads to loss of overlying photoreceptors
- Active area of basic science and clinical research

**Advanced Dry AMD: Geographic Atrophy (GA)**

- Loss of photoreceptors & RPE

![Fundus Photograph](Image)

- Photoreceptors
- RPE
- Bruch’s membrane
- Drusen
- Choriocapillaris

**Is Geographic Atrophy on the Rise?**

- Usually progresses slowly over years, often sparing the foveal center until late
- Increases with increasing age
  - Age > 50: 0.6%
  - Age > 75: 3.5%
  - Age > 90: 22%
- Natural evolution of AMD often overshadowed by exudative dz

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Roth. Graefes, 2004
Sunness. Retina, 2007
Geographic Atrophy

Correlation of atrophy in FAF images with photoreceptor drop-out

Atrophy Progression
Dry ARMD
previously not so sexy....

However things are changing.....

Geographic Atrophy

2010 2015

- Growth Rate ≈ 1.78 mm²/year
- Median time to central GA after any GA ≈ 2.5yr

Geographic Atrophy Phase III Trial
SPECTRI

- Lampalizumab (anti-factor D trial) (injection)
  - Phase III
  - Phase II Mahalo results: 30% reduction in GA growth with drug
  - 2 yr study
  - Hope and promising!
Anti-VEGF Treatments
The Big 3

- Wet ARMD
- Diabetic Retinopathy
- Retinal Vein Occlusions (BRVO/CRVO)
What is Vascular Endothelial Growth Factor (VEGF)?

- naturally occurring protein
- stimulates angiogenesis
- triggers vascular permeability
- pro-inflammatory

Angiogenesis

- Choroidal neovascularization (CNV)/ AMD
- Diabetic retinopathy
- Retinal vein occlusion
- Retinopathy of prematurity
- Corneal neovascularization
- Iris neovascularization
Wet Exudative AMD

Growth of Abnormal Vessels
Endstage AMD

Wet AMD: Evolution of Treatment

Macular Photocoagulation Study (MPS)-1991-1995

*While on active treatment
Prevention of Moderate Vision Loss

- Stability
  - Could mean loss of 0 letters or actual gain
  - Often meant loss of less than 3 lines

3-line gainers

- Represent true visual gain
- Accepted by FDA as clinically significant
Home Runs = 3 Line Gainers

3 Line Losers
Macular Photocoagulation Study (MPS)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treated Eyes (%)</th>
<th>Untreated Eyes (%)</th>
<th>Years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTRA-FOV</td>
<td>48%</td>
<td>62%</td>
<td>5</td>
</tr>
<tr>
<td>JUXTA-FOVEA</td>
<td>52%</td>
<td>61%</td>
<td>4</td>
</tr>
<tr>
<td>SUB-FOVEA</td>
<td>22%</td>
<td>47%</td>
<td>4</td>
</tr>
</tbody>
</table>

Wet ARMD Treatment Circa 2001- PDT

Big Losers & Home Runs Classic CNVM

<table>
<thead>
<tr>
<th></th>
<th>Big Losers (%)</th>
<th>Home Runs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural History</td>
<td>69%</td>
<td>2%</td>
</tr>
<tr>
<td>Valsalva</td>
<td>47%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>
Pegaptanib Slows Vision Loss

**Study EOP 1003**

<table>
<thead>
<tr>
<th>Week</th>
<th>Vision (letters)</th>
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<tbody>
<tr>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
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<td>18</td>
<td>45</td>
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<td>24</td>
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<td>30</td>
</tr>
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<td>84</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>102</td>
<td>0</td>
</tr>
</tbody>
</table>

Patient Treatment (Year 1) vs (Year 2)
- (0.3 mg)
- (Sham)

Sham or discontinue

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Big Losers & Home Runs

**Classic CNVM**

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<td>Macugen</td>
<td>41%</td>
<td>6%</td>
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Ranibizumab (Lucentis)

- Anti-VEGF
- Antibody fragment
- FDA-approved for wet AMD (June 2008)
- Groundbreaking results in phase III clinical trials
- Marina and Anchor compared against sham & PDT
- Newer trials investigating higher dose (HARBOR)
  - Does higher dose result in extended action?
Mean Change in VA Over Time

Sham (n=238) Ranibizumab 0.3 mg (n=238) Ranibizumab 0.5 mg (n=240)

Secondary Endpoint: Mean Change in Visual Acuity Over Time

Note: Vertical bars are ± one standard error of the mean.

*P<0.0001 (Rounded values)
Big Losers & Home Runs
Classic CNVM

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<td>6%</td>
</tr>
<tr>
<td>Lucentis</td>
<td>8%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Bevacizumab (Avastin)

- Anti-VEGF antibody
- Approved for colorectal cancer (IV)
- Off-label use in ocular neovascular diseases
- Specialty pharmacy prepares doses
- Genentech (same as Lucentis)
The Bevacizumab Avastin Revolution

May 2005 ASRS- Rosenfeld

Intravitreal bevacizumab (Avastin™)

- Bevacizumab is FDA approved for metastatic colorectal cancer
- Not supposed to work since Genentech study showed no penetration in the primate retina
- Extensive primate studies in mid 1990s
  - Blocked neovascular glaucoma in a primate model
  - No adverse effects to the retinal morphology noted
  - But never directly tested as treatment of CNV

Clinical Trials for Wet AMD: CATT Trial

- CATT: Comparison of AMD Treatment Trial
  Multicenter, NEI-sponsored non-inferiority trial
  Avastin versus Lucentis, dosing strategies
  - Completed April 2011, published NEJM
  - At year two now, equal effects when q month
  - PRN arms did significantly worse
  - Avastin has more serious adverse effects?
  - Cost Differential
  - RCH among biggest sites
What about persistent SRF or cysts?

That dog don’t hunt.

VEGF Trap

- Smaller than an antibody (MW ~110,000)
- Binds VEGF tighter than native receptors, monoclonal antibodies or aptamers
- Blocks VEGF and placental growth factor (PLGF)
- Systemic half life in humans ~ 25 days

- Eylea became available for ARMD November 2011
- Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgGFc
- Blocks all VEGF-A isoforms and placental growth factor (PlGF)
- High affinity - binds VEGF-A and PlGF more tightly than native receptors
- Contains all human amino acid sequences

**VEGF Trap-Eye: afiblercept (Eylea)**

**VEGF Trap-Eye: A Unique VEGF Blocker**

- Fusion protein
- VEGF R1
- VEGF R2
- All human a.a. sequences
- High affinity
- Blocks all VEGF-A & PlGF

**Proportion of Patients who Gained Vision at Week 52**

Compared to baseline: LOCF, Full analysis set: Rq4 n=595; 2q4 n=613; 0.5q4 n=597; 2q8 n=607
OCT Identifies VEGF-Induced Exudation: OCT Is a VEGF-Meter

Cirrus Spectral Domain OCT image through central macula

VA: 20/100

VEGF induces macular fluid
- Intraretinal fluid
- Subretinal fluid
- Sub-RPE fluid (PED)

What we do not want – Endstage AMD

Is there anything better than just Anti-VEGF? What’s New?

FOVISTA™ (E10030) Binds to PDGF and Strips Pericytes

Anti-PDGF

Pericytes

Endothelial Cells

Mitchell et al., Angiogenesis 28 November 2007

Phase 2b Study Results

MEAN CHANGE IN VISUAL ACUITY (VA) (BASELINE TO WEEK 24)

ECLIPSE
ARGUS II Retinal Prosthesis
The Bionic Eye

Lieutenant Commander Geordi La Forge

Retinitis Pigmentosa

Progressive inherited disease
≈ 200,000 Americans
≈ 500 in Greater Houston: LP or NLP

Argus II Retinal Prosthesis
Thank you!
Keep an eye out for more AMD therapies… they are fantastic and are coming soon!