Macular Degeneration

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Dry Macular Degeneration (Non-neovascular AMD)

- Aging and thinning of macular tissue with pigmentary changes in the macula
- Gradual loss of central vision may occur but is usually not as severe as the symptoms associated with wet AMD

Amsler Grid
**Epidemiology of AMD in USA**

- With aging of population AMD is reaching epidemic proportions.
- Currently
  - Accounts for 16% of all causes of blindness
  - 7.3 million with some form of AMD
  - 1.75 million with wet or advanced AMD
  - Annual direct cost of AMD in USA estimated at $10 billion
- Projection for 2020
  - 2.95 million with wet or advanced AMD

_Venkataraman K et al. Invest Ophthalmol Vis Sci E-Abstract 3089 2003_  

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**Risk Factors**

1. **Age**
   - Advanced AMD: 60s- <1%
   - 90s- 15%

2. **Female gender**

3. **Caucasian, Oriental Race** more likely to progress to neovascular AMD

4. **Smoking (>10 pack-years)**
   - Directly related with 15% of cases
   - Living with a smoker doubles risk of developing AMD

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**Prevalence of all (dry and wet) AMD by Age Group**


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**Risk Factors**

5. **Positive family history**

6. **Hypertension**

7. **Obesity and Inactivity**-higher BMI
   - more than double risk compared with vigorous activity 3x/week

8. **Inflammatory biomarkers**
   - C-reactive protein, interleukin 6
   - Complement Factor H variant
Not Risk Factors

- Light Eye Color
- People age 60 and over with no AMD have very low risk for developing AMD progression after 10 years of follow-up

Components of Dry AMD

1. Soft drusen
2. RPE hyperpigmentation
3. RPE hypopigmentation/atrophy
4. Geographic atrophy

Soft Drusen

- Yellow deposits which lie under the RPE within Bruch's membrane
- Represent accumulated waste products from outer retinal layers
- A marker for macular degeneration
- There is increased risk for developing AMD as the number of drusen increases
Hard Drusen

- Small in size (<63 microns), not part of AMD definition because a constant retinal finding after 5th decade
Age 48

Age 52

Age 57

RPE Hyperpigmentation

- Pigment clumping within the retinal pigment epithelium
RPE Hypopigmentation

- Atrophy of the retinal pigment epithelium

Geographic Atrophy

- Sharply delineated area of hypo- or depigmentation with absence of the RPE

Age 68
20/25

Age 69
20/30

Age 73
20/80
FUNDUS AUTOFLUORESCENCE (FAF)

- Permits mapping of atrophic changes as well as lipofuscin accumulation in the RPE layer.
- Lipofuscin in RPE cells represents a common pathogenetic pathway for various retinal dystrophies and degenerations including AMD.
- FAF RPE lesion characteristics and their progression has prognostic implications.

FAF Imaging

Progression of Geographic Atrophy Over 6.5 Years
**Definition of Early Age-Related Maculopathy**

1. Age >50
2. Soft drusen (>63 microns). Those with indistinct margins, drusen >125 microns are more significant
3. Areas of RPE hyperpigmentation associated with drusen
4. Areas of RPE hypopigmentation associated with drusen

**Not in Definition of Early Age-Related Maculopathy**

- Visual acuity since advanced changes may be present without affecting visual acuity
- Small hard drusen (<63 microns) since a constant finding after 5th decade
- Pigmentary changes unassociated with drusen since other processes can cause these

**Differential Diagnosis of Dry Macular Degeneration**

**Foveomacular Pattern Dystrophy (Adult Vitelliform)**

- Autosomal dominant
- Bilateral and symmetric
- Very slowly progressive
- Age of onset of symptoms is between 30-50 years
- Excellent visual prognosis (VA: 20/20 to 20/40)
Central Hyperfluorescent Lesion

Autosomal dominant
• Bilateral and symmetric
• Very slowly progressive
• Age of onset of symptoms is between 30-50 years
• Excellent visual prognosis (VA: 20/20 to 20/40)

62 YOF with VA: 20/25 OU
• Had been diagnosed with dry AMD for previous 10 years but wanted a second opinion
MYOPIC DEGENERATION

- Progressive elongation of the eye with thinning of choroid and RPE
- High myopia: >-6.00 D
- Often excellent acuity despite extensive chorioretinal atrophy

CENTRAL AREOLAR CHOROIDAL DYSTROPHY (CACD)

- Autosomal dominant
- Bilateral and symmetric
- Slowly progressive
- Age of onset: 2nd-4th decades
- Central vision affected 4th-5th decades
- VA: 20/100-20/200 by 7th to 8th decades

Therapeutic Strategies for Dry AMD

- Since retinal cells are neural cells, we can’t substitute them
- Therefore, currently our best therapeutic strategy is to maintain the available retinal cells in a healthy state
- Antioxidant vitamins and zinc have previously shown promise in retarding AMD progression in several pilot trials

AREDS
Age-Related Eye Disease Study
### Goals
- **Clinical Trial**
  - To evaluate the effects of nutritional supplements on the progression of both AMD and cataract

### AREDS
- Took 2 tablets twice a day
- Followed an average of 6.7 years
- Randomly assigned to 1 of 4 different treatment groups

<table>
<thead>
<tr>
<th>AREDS</th>
<th>The Treatment Groups</th>
</tr>
</thead>
</table>
| • 4757 participants (Sept 1990-Jan 1998)  
• Largest randomized clinical eye trial ever conducted  
• Findings have had an enormous public health impact on the treatment of dry AMD globally |  
1. **Zinc and copper alone** (copper used since high zinc levels can cause Cu deficiency)  
2. **Antioxidants alone**: b-carotene (vitamin A), Vitamins C and E  
3. **Combination of antioxidants and zinc**  
4. **Placebo** (a look-a-like pill that had no active ingredient) |
**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size 2 Capsules</th>
<th>Servings Per Container 30</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>25,000 IU</td>
<td>500%</td>
</tr>
<tr>
<td>(100% as beta-carotene)</td>
<td>15 mg</td>
<td></td>
</tr>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>500 mg</td>
<td>833%</td>
</tr>
<tr>
<td>Vitamin E (d-alpha tocopheryl succinate)</td>
<td>400 IU</td>
<td>1333%</td>
</tr>
<tr>
<td>Zinc (zinc oxide)</td>
<td>60 mg</td>
<td>533%</td>
</tr>
<tr>
<td>Copper (cupric oxide)</td>
<td>2 mg</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Category 1 – No AMD
  - These participants had no drusen or only a few small drusen (<63 microns) in one or both eyes

- Category 2 – Early AMD
  - These participants had several small drusen or a few medium-sized drusen (63-125 microns), in one or both eyes
**Category 3 – Intermediate AMD**

- These participants had many medium drusen or one or more large drusen (>125 microns), or areas of atrophy (thinning) of the tissue outside the central macula in one or both eyes.

**Category 4 – Advanced Unilateral AMD**

- These patients had
  - Geographic atrophy involving macula center
  - Neovascular AMD in one eye
5 Year Results

Chances of Developing Advanced AMD

- Category 2 (Early AMD), less than 2%
- Category 3 (Intermediate AMD), 18%
- Category 4 (Advanced AMD one eye), 43%

Proportion of Participants with Loss of 15 or More Letters in At Least 1 Study Eye in Categories 3 and 4

Conclusions of AREDS
• Early AMD-No benefit of Rx, observe
• Intermediate or advanced AMD: recommend AREDS supplements

Other General Recommendations:
• Stop smoking
• Control hypertension
• Wear ultraviolet lens protection
• Amsler grid self-testing

After Cataract Surgery
• AREDS did not show
  ✓ Increased risk of developing wet AMD
  ✓ Development of geographic atrophy

Side Effects of Vitamins
• Beta-carotene
  ✓ Yellowing of skin
  ✓ Increased risk of death in smokers
  ✓ High levels may lead to osteoporosis

• Zinc
  ✓ Genitourinary problems requiring hospitalization-UTI, stress incontinence and prostatic hyperplasia (7.5% vs 5%)
  ✓ Anemia (13% vs 11% not taking Zn)

• Vitamin E
  ✓ Avoid if on anticoagulants or bleeding diathesis

Supplement Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Ocuve Preservision (4/day)</th>
<th>Preservision with Lutein (2/day)</th>
<th>Ocular Nutrition (4/day)</th>
<th>Ocuve with Lutein (1/day)</th>
<th>Centrum Silver (1/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>28,640</td>
<td>None</td>
<td>20,000</td>
<td>1,000</td>
<td>5000</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>452 mg</td>
<td>452 mg</td>
<td>1200 mg</td>
<td>200 mg</td>
<td>60 mg</td>
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<tr>
<td>Vitamin E</td>
<td>400 IU</td>
<td>400 IU</td>
<td>440 IU</td>
<td>60 IU</td>
<td>45 IU</td>
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<tr>
<td>Zinc</td>
<td>69.6 mg</td>
<td>69.6 mg</td>
<td>60 mg</td>
<td>40 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>1.6 mg</td>
<td>1.6 mg</td>
<td>None</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Lutein*</td>
<td>None</td>
<td>10 mg</td>
<td>10 mg</td>
<td>2 mg</td>
<td>0.25 mg</td>
</tr>
</tbody>
</table>
AREDS 2 Trial

Goals

1. Evaluate the effects of dietary xanthophylls and omega-3 fatty acids on the development of advanced AMD
2. Study the effects of eliminating beta-carotene in the original AREDS formula on AMD development and progression
3. Study the effects of reducing zinc in the original AREDS formula on AMD development and progression
4. Study the effects on cataract and moderate visual loss

Retinal Xanthophylls: Lutein and Zeoxanthin

- Lutein represents 36%, zeaxanthin 18% of natural carotenoids in the macula
- Not used in AREDS I since they were not readily available for research formulation at the time
- Shown to protect against progression of AMD in 5/6 pilot studies

Highest Dietary Sources of Lutein and Zeaxanthin

- Kale
- Collard Greens
- Orange peppers
- Spinach
- Fresh parsley
- Orange Juice
- Egg yolk
- Various squash
- Kiwi
- Zucchini
- Mustard greens
- Grapes

*In general, the most colorful fruits (dark green, orange, yellow) have the highest carotenoids*
**Omega-3 Fatty Acids:**

- Docosahexaenoic acid (DHA)
- Eicosapentaenoic acid (EPA)

<table>
<thead>
<tr>
<th>AREDS 2 Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,000 participants</td>
</tr>
<tr>
<td>Recruitment completed on June 30, 2008</td>
</tr>
<tr>
<td>5-year follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest Dietary Sources of Omega-3 Fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild salmon</td>
</tr>
<tr>
<td>Herring</td>
</tr>
<tr>
<td>Mackerel</td>
</tr>
<tr>
<td>Anchovies</td>
</tr>
<tr>
<td>Sardines</td>
</tr>
<tr>
<td>Fish oil supplements</td>
</tr>
</tbody>
</table>

**AREDS found an association between greater fish intake and 40% reduced AMD progression**

- Mouse retinopathy model
  - Mice on omega-3-rich diet had 40-50% decrease in pathologic vessel growth

**AREDS 2 Clinical Trial**

- Neovascular (wet) AMD:
  -Leading cause of vision loss in elderly
- Choroidal neovascularization (CNV)
- Vascular leakage
- Progressive loss of central vision
- 10% have wet AMD
- 153,000 new advanced cases each year in US
  - Advanced: geographic atrophy, Neovascularization

**Wet AMD**
Wet AMD

- Symptoms
  - Blurred vision
  - Scotoma
  - Metamorphopsia
  - Micropsia
  - Dyschromatopsia

![Normal Distortion Scotoma Blur Scotoma](image1)

![image2]

![image3]

![image4]
Choroidal Neovascular Membrane

- **Composition**
  - Classic: well defined pattern
  - Predominantly classic ≥ 50% classic CNV
  - Minimally classic < 50% classic CNV
  - Occult: poorly defined pattern
- **Size and Boundaries**
- **Location**
  - Extrafoveal > 200 microns from foveal center
  - Juxtafoveal 1-199 microns from foveal center
  - Subfoveal

Occult CNV

- **Fibrovascular Pigment Epithelial Detachment**
  - Irregular elevation of retinal pigment epithelium
  - Hyperfluorescent stippling 1-2 minutes into FA
  - May or may not show leak in lates
- **CNV**
  - Late leakage of undetermined source
  - Speckled hyperfluorescence in lates
  - Pooling around speckles

**Classic CNV**

- Well defined
- Early hyperfluorescence
- Progressive hyperfluorescence
- Fluorescence extends beyond initial boundaries
- Pooling of Fluorescein late

Courtesy of Digital Angiography Reading Center (DARC), New York NY
Angiogenic Cascade

Pharmacologic Treatment of Wet AMD

- Photodynamic Therapy with Verteporfin
- Anti-VEGF Therapy (Macugen, Lucentis and Avastin)

Photodynamic Therapy (PDT)

- Effect based on photosensitivity of verteporfin and its selective uptake by neovascular or neoplastic cells
- Visudyne was approved by FDA in 2000: the first drug treatment for wet AMD
- Other uses: esophageal, lung, pancreatic and bile duct CA, acne, rosacea and psoriasis
- Other FDA-approved photosensitizers include Metvix, LS11, Photofrin and Levulan
Mechanism Of PDT

- The photosensitive molecule (Verteporfin) or a metabolic precursor is activated at its maximum absorbance $\lambda$ (692 nm)
- The photosensitive molecule returns to a grounded state releasing energy that excites oxygen present in local tissue
- Highly reactive singlet and superoxide oxygen radicals are formed which destroy the proliferative tissue that has absorbed the photosensitive molecules (vascular endothelium)

2 Clinical Trials: TAP and VIP

TAP Trial: Treatment of ARMD with PDT

- PDT reduced risk of moderate vision loss in predominantly classic lesions
- Rx was q 3 months: indicated by presence of leakage on FA
- $n=609$ (207 placebo)
- Lost greater than 3 lines of visual acuity

<table>
<thead>
<tr>
<th>PDT-treated</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 12 months:</td>
<td>39% 54%</td>
</tr>
<tr>
<td>At 24 months:</td>
<td>47% 62%</td>
</tr>
</tbody>
</table>

*Greater benefit if classic portion occupied >50% of lesion
*Trial continued to 60 months as uncontrolled, open-label treatment and showed sustainment of 24 month outcomes
VIP Trial: Verteporfin in PDT

- PDT reduced the risk of moderate to severe vision loss in cases of occult with no classic CNVM
- n=225 Occult CNV (not originally eligible for TAP study)

Lost greater than 3 lines of visual acuity:

<table>
<thead>
<tr>
<th></th>
<th>PDT-treated</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 12 months</td>
<td>49%</td>
<td>45%</td>
</tr>
<tr>
<td>At 24 months</td>
<td>55%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Lost greater than 6 lines of visual acuity:

<table>
<thead>
<tr>
<th></th>
<th>PDT-treated</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 12 months</td>
<td>22%</td>
<td>33%</td>
</tr>
<tr>
<td>At 24 months</td>
<td>29%</td>
<td>47%</td>
</tr>
</tbody>
</table>

- *Greater benefit with smaller lesions or VA > 20/50
- *Trial continued to 60 months as uncontrolled, open-label treatment and showed sustainment of 24 month outcomes

Side Effects of Visudyne PDT

- Mild to moderate, transient and include
  - Injection site reactions: pain, edema, extravasation,
  - Severe vision decrease: > 4 lines due to choroidal ischemia reported in 1%-5%. Incidence greatly decreased with reduced fluence PDT
  - Skin Photosensitivity to sunlight, halogen light
  - Back pain resolves by end of infusion

After Treatment

- Since verteporfin can cause porphyrin-induced skin damage and photosensitivity (due to reactive O₂ species), we ask patients to avoid exposure to sun or bright indoor lighting for 5 days and wear
  - Long-sleeved shirt
  - Long pants shoes and socks
  - Dark sunglasses
  - Wide-brimmed hat
  - Gloves
- *Exposure to normal indoor light is needed to help inactivate Visudyne in the skin.
Anti-VEGF Therapy

Vascular Endothelial Growth Factor

- Member of a family of growth factors
  - VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF
- Homodimeric glycoprotein secreted by a variety of cells
- Receptor-binding domain: essential for receptor-VEGF-A interaction and its role in triggering angiogenesis
- Initiates the angiogenic cascade by binding to VEGF receptors on the surface of endothelial cells

Pegaptanib Sodium

- Macugen
- Selective VEGF-A<sub>165</sub> inhibitor
- Indicated for neovascular AMD
- FDA approved December 2004

Ranibizumab and Bevacizumab

- Human Anti-VEGF-A MAb (~150 kDa)
- Human Fab framework
- FDA approved June 2005

MARINA and ANCHOR Trials

**MARINA**: Phase III, multicenter, randomized, double-masked, sham-controlled study

**ANCHOR**: Phase III, multicenter, randomized, double-masked, active-controlled study

Patients with minimally classic or occult lesions (N=716)
- Sham injection monthly (n=238)
- LUCENTIS 0.3 mg monthly (n=240)

 Patients with predominantly classic lesions (N=423)
- LUCENTIS 0.3 mg monthly + sham PDT every 3 months as needed (n=140)
- LUCENTIS 0.5 mg monthly + sham PDT every 3 months as needed (n=140)

- Verteporfin PDT on day 0 and every 3 months as needed + injection monthly (n=143)

- Sham injection monthly (n=238)

The 0.3 mg dose was not included in the FDA label. Therefore, efficacy results on the following slides reflect only the 0.5 mg dose.


**Up to 41% Improved Vision at 2 Years**

MARINA
- Ranibizumab 0.5 mg (95% CI=16%, 34%)
- Sham

- Primary endpoint: <15-letter loss from baseline

ANCHOR
- Ranibizumab 0.5 mg (95% CI=29%, 44%)
- Verteporfin PDT

- Secondary endpoint: ≥3 line gain from baseline

- Up to 42% with 20/40 or better, 2 Years

- Ranibizumab 0.5 mg (95% CI=16%, 34%)
- Sham


**90% Maintained Vision at 2 Years**

MARINA
- Ranibizumab 0.5 mg (95% CI=16%, 34%)
- Sham

- Primary endpoint: <15-letter loss from baseline

ANCHOR
- Ranibizumab 0.5 mg (95% CI=29%, 44%)
- Verteporfin PDT

- Up to 42% with 20/40 or better, 2 Years

- Ranibizumab 0.5 mg (95% CI=16%, 34%)
- Sham


**MARINA: Mean Change in VA**


**PIER Trial Design**

Phase IIIb, multicenter, randomized, double-masked, sham-controlled study

- Subfoveal CNV ± Classic component (N=334)
- Randomization 1:1:1
- Monthly x 3, then every 3 months

**ANCHOR: Mean Change in VA**


**PIER: Mean Change in VA**

### Ocular Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ranibizumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>43 - 77%</td>
<td>29 - 66%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>17 - 37%</td>
<td>11 - 33%</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>3 - 10%</td>
<td></td>
</tr>
<tr>
<td>Increased intraocular pressure</td>
<td>8 - 25%</td>
<td>3 - 8%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>7 - 22%</td>
<td>13 - 22%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>5 - 11%</td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>5 - 20%</td>
<td>6 - 16%</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>6 - 19%</td>
<td>6 - 14%</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>4 - 19%</td>
<td>6 - 20%</td>
</tr>
<tr>
<td>Increased lacrimation</td>
<td>3 - 17%</td>
<td>0 - 16%</td>
</tr>
</tbody>
</table>

### Arterial Thromboembolic Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sham (n=236)</th>
<th>Ranibizumab (n=477)</th>
<th>PDT (n=143)</th>
<th>Ranibizumab (n=277)</th>
<th>Sham (n=42)</th>
<th>Ranibizumab (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal hemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>3.8% (9)</td>
<td>4.6% (22)</td>
<td>4.2% (6)</td>
<td>4.7% (13)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Serious Ocular Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>MARINA (Year 2)</th>
<th>ANCHOR (Year 2)</th>
<th>PIER (Year 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis</td>
<td>0</td>
<td>1.0% (5)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0.4% (1)</td>
<td>0.7% (1)</td>
<td>0.7% (2)</td>
</tr>
<tr>
<td>Iatrogenic traumatic cataract</td>
<td>0</td>
<td>0.2% (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Safety data pooled from MARINA (Year 2), ANCHOR (Year 2) and PIER (Year 1).
Summary: Clinical Trials

• All CNV lesions types
• At up to 2 years with monthly dosing,
  ✓ Vision maintained in up to 90% of patients
  ✓ Vision improved (≥15 letters) in up to 42% of patients
• Reduced-interval dosing better than natural history
• Low incidence of serious ocular events (<0.1%)

• With the advent of anti-VEGF agents patients with wet AMD are receiving better treatment than ever
• Pan-anti-VEGF agents alone have been shown to be far superior to PDT alone in treating wet AMD

Injection Video

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

• 1:1:1 (0.3 or 0.5 mg of lucentis or PDT)
• n=423
• Lost greater than 15 letters:
  ✓ 5.7% given 0.3 mg of lucentis
  ✓ 3.6% given 0.5 mg of lucentis
  ✓ 35.7% given verteporfin
• Gained by 15 or more letters:
  ✓ 35.7% given 0.3 mg of lucentis
  ✓ 40.3% given 0.5 mg of lucentis
  ✓ 5.6% given verteporfin
• Conclusion: Ranibizumab was far superior to verteporfin

• However, intravitreal injections are required in 4-6 week intervals with frequent follow-up visits
• There are substantial 3rd party payer expenses
• As a result, PDT has been revisited as a complementary treatment to anti-VEGF monotherapy

**Current Clinical Trials**

- Novartis: n=323, 43 centers; avastin/PDT vs avastin alone
- RADICAL Study: n=160, 26 centers; lucentis vs double Rx vs triple Rx (IVD)
- Oklahoma State University: n=30, lucentis vs double Rx
- Texas Retina Associates: n=60, lucentis vs double Rx
- Basel, Switzerland: n=40, lucentis vs double Rx
- San Francisco (Bay Area Associates): n=60, triple RX (IVD) vs lucentis alone
- Houston (Greater Houston Retina): n=30, avastin vs double Rx

**Combination Treatment with PDT and Intravitreal Anti-VEGF Agents**

- Gives two synergistic mechanisms of action
- Can reduce treatment frequency vs anti-VEGF monotherapy
- Reduced (half) fluence (25 Joules / 300 mW per cm2) is used to minimize collateral damage