Current Treatment of Age Related Macular Degeneration

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Financial Disclosure

I have financial interest/agreement or affiliation with Lansing Ophthalmology, where I am a shareholder and employed as a retina specialist.
Macular
Macular

- Center of retina
- Small – 5-6 mm in diameter
- Responsible for detailed central vision/fine details
Optical coherence Tomography
Age related macular degeneration (AMD)

- Chronic condition
- Affects the macular
- Causes central vision loss
- Leading cause of vision loss among adults over age 60 in the US
Epidemiology
National Health and Nutrition Examination Survey (NHANES)

- Total prevalence over 40 yrs old
  - Any AMD - 6.5% (7.2 million people)
  - Late stage of AMD – 0.8% – (809,000)
  - Statistically significant lower prevalence of any AMD in blacks cp to whites

Age Related Macular Degeneration (AMD)

• Spectrum of diseases
• Two major subtypes

  – Dry AMD
    • Atrophic
    • Non-exudative
    • Non-neovascular

  – Wet AMD
    • Neovascular

  – There is also a group of patients who experience exudation without neovascularization
DRY- Non-exudative AMD

- Drusen
- Pigmentary alterations,
- Atrophy of the RPE and choroid.
DRY- Non-exudative AMD

- Drusen
  - small or hard drusen
  - large or soft/exudative drusen
  - basal laminar or cuticular drusen
  - mineralized or calcified drusen
  - reticular pseudodrusen
Drusen

• Clinically, drusen size can be compared to the width of a major vein at the disc edge (approximately 125 µm).
DRY- Non-exudative AMD

- Small or hard drusen
  - <63 μm in size (< 0.5 major vein width)
  - Small yellow-white lesions
  - Distinct borders
  - Located at the level of Bruch's membrane
  - Common in people over 40 years of age and by
  - Not high risk for progressive loss of central vision.
Small Drusen
DRY- Non-exudative AMD

• **Medium-sized drusen**
  - 63–124 μm in size.
  - > 0.5 < 1.0 major vein width
DRY- Non-exudative AMD

- Large or soft drusen
  - 125 μm or greater
  - Indistinct borders
  - Associated with an increased risk of pigment abnormalities, geographic atrophy, and choroidal neovascularization.
Large Drusen
DRY- Non-exudative AMD

• Geographic atrophy (GA)
  • Discrete areas of RPE and choriocapillaris loss
  • At least 175 μm in diameter
  • Choroidal vessels are often visible
  • Window defect on FA
  • Dark on FAF
Geography Atrophy (GA)
GA
GA
Wet - Neovascular AMD

• Retinal neovascularization
• Choroidal neovascularization (CNV)
• Serous and hemorrhagic complications.
Pathogenesis

- CNV appears as a neovascular sprout growing under or through the RPE through breaks in Bruch's membrane

Pathogenesis

• Usually this occurs in association with evidence of fibroblasts, myofibroblasts, lymphocytes, and macrophages.

• Various growth factors are suspected to be involved in the development of this CNV, such as vascular endothelial growth factor (VEGF).


Classification of CNV

• Type 1 (occult) CNV
  • Under the retinal pigment epithelium (RPE)
  • Less distinct
  • Less permeable
  • Less actively proliferating
  • Poorly defined leakage on FA
Classification of CNV

• Type 2 (classic)

  • Choroidal vessels have penetrated the retinal pigment epithelial complex gaining access to the subretinal space.

  • Actively proliferates beneath the neurosensory retina

  • Well-demarcated intense leakage associated with dye pooling on FA

  • Intensely fluorescent during the recirculation phase.

  • Lacy bright pattern of early angiographic filling
Mixed Neovascularization

- Majority of cases
- Predominantly occult and classic
- Minimally occult and classic
Classification of CNV

• Type 3 – Retinal angiomaticous proliferation (RAP)
  – Third anatomic subtype of neovascularization
  – New vessels within the retina itself
  – Compensatory telangiectatic response,
  – A perfusing arteriole,
  – A draining venule,
  – Retinal–choroidal anastomosis.

Polypoidal Choroidal Vasculopathy (PCV)

- Variant of type 1
- Sub-pigment epithelial area
- Branching inner choroidal vessels
- Terminal aneurysmal changes

Clinical grading of AMD

• Features are evaluated within 3000 µm of the center of the macula

Clinical grading of AMD

• No AMD
  – No Drusen or few < 15 small drusen in the absence of any other stage of AMD
Clinical grading of AMD

• Early AMD
  – Extensive (>15) small drusen
  – Few (approximately <20) medium-size indistinct drusen (soft borders)
  – Pigment abnormalities (increased pigmentation or depigmentation but not geographic atrophy) and no other stage of AMD.

Early AMD
Clinical grading of AMD

- **Intermediate AMD**
  - Presence of at least one large druse
  - Numerous medium-size drusen
    - 20 or more when the drusen boundaries are amorphous
    - 65 or more when the drusen boundaries are distinct, sharp or hard
  - Geographic atrophy that does not extend under the center of the macula (noncentral GA).

Intermediate AMD
Intermediate AMD
Clinical grading of AMD

• **Advanced stage of AMD**
  – Geographic atrophy extending under the center of the macula
  – Neovascular AMD.

Advanced AMD
Advanced AMD
Diagnostic Tools

• Fundus photography (FP)
• Fluorescein angiography (FA)
• Optical Coherence Tomography (OCT)
• Fundus Auto Fluorescence (FAF)
• Indocyanin green Angiography (ICG)
Fundus photography (FP)
Fluorescein angiography (FA)
Optical Coherence Tomography (OCT)
Fundus Auto Fluorescence (FAF)
Indocyanin green Angiography (ICG)
MANAGEMENT OF NON-NEOVESSEL AMD
Management Of Non-Neovascular AMD

• Annual evaluation of the retina to determine the presence and stage of AMD.
Management Of Non-Neovascular AMD

• If no AMD then no intervention
• If early AMD then annual follow up
  – One third progress to intermediate AMD in first 5 yrs of follow up
  – Vitamin supplements not beneficial

Management Of Non-Neovascular AMD

• If intermediate AMD
  – Consider AREDS type dietary supplement (if no medical contraindication)
    • Daily dose of
      – 500 mg vitamin C
      – 400 international units of vitamin E
      – 15 mg beta carotene (non-smokers)
      – 80 mg zinc oxide
      – 2 mg cupric oxide (to reduce the risk of a copper-deficiency anemia).

Management Of Non-Neovascular AMD

- Unilateral intermediate AMD on the AREDS 1 formulation
  - Decreased risk of progression to advanced AMD
  - Decreased risk of vision loss through at least 10 years

Probability of Advanced AMD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probability of AMD Event by Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
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<tr>
<td>Placebo</td>
<td>.142</td>
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<tr>
<td>Antioxidants</td>
<td>.112</td>
</tr>
<tr>
<td>Zinc</td>
<td>.106</td>
</tr>
<tr>
<td>Antioxidants + Zinc</td>
<td>.098</td>
</tr>
</tbody>
</table>
Management Of Non-Neovascular AMD

• AREDS 2
  – Oral supplementation with
    • Lutein
    • Zeaxanthin
    • Omega-3 fatty acids
    • Among individuals with bilateral intermediate AMD or those with unilateral advanced AMD with large drusen in the healthier contralateral eye
Management Of Non-Neovascular AMD

- No additional benefit over AREDS 1 (non smokers)
- Safe for smokers
- Possible standardization benefit (1/2 of AMD pts are former smokers)

LuteinZeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial : http://jama.jamanetwork.com
AREDS and Advanced AMD

• If unilateral advanced AMD
  – GA
  – Neovascular AMD
  – Disciform scar
  – fellow eye is at high risk of progression to advanced AMD
  – Consider AREDS vitamin to decrease anatomic progression and functional impairment.

AREDS and Advanced AMD

• Unilateral advanced AMD on the AREDS 1 formulation
  – Decreased risk of progression to advanced AMD
  – Decreased risk of vision loss through at least 10 years

AREDS and Advanced AMD

• If bilateral advanced AMD
  – Consider AREDS type supplement if visual acuity is relatively good (20/100 or better) in at least one eye in the presence of CNV.
  – Decreased risk of at least 3 additional lines of visual acuity in the eye with neovascular AMD among the advanced AMD participants with unilateral CNV at baseline.

MANAGEMENT OF NEOVASCULAR AMD
HISTORY

- LASER
- SURGERY
- PDT
- Anti VEGF
LASER

- Laser photocoagulation has been shown to be beneficial for some lesions
  - well-defined lesions not involving the foveal center

- Additional visual acuity loss can occur
  - recurrent CNV
  - treatment will destroy retinal tissue (and corresponding function).

SURGERY

- Submacular surgery
- Macular translocation
- Vitrectomy
  - Tpa
  - Gas
Submacular surgery

• Visual acuity outcomes with submacular surgery are no different compared with observation for subfoveal CNV in patients with AMD in which a majority of the lesion is CNV and there is evidence of classic CNV.

Macular translocation

• No strong evidence on
  – Effectiveness
  – Technique

• Significant rate of complications

• Randomized clinical trials are needed
Subretinal Recombinant Tissue Plasminogen Activator (rt-PA)

• Useful in displacing thick submacular hemorrhage

• More controlled studies needed.

Photodynamic Therapy (PDT)

- Intravenously injected photosensitizing drug
- Low-intensity laser light
- Photochemical reaction
- Direct cellular injury, including damage to vascular endothelial cells and vessel thrombosis
- Damage of choroidal neovascular tissue

PDT

• The TAP Study Group
  – PDT with verteporfin (Visudyne) can reduce the risk of moderate and severe visual acuity loss for at least 2 years
  – Predominantly classic subfoveal lesions

Verteporfin In Photodynamic therapy (VIP) Trial

– Occult with no classic lesions with recent progression
  • blood associated with CNV
  • Definite loss of visual acuity within the past 3 months
  • Growth of the lesion on fluorescein angiography

– PDT could reduce the risk of moderate (3 lines) and severe visual acuity loss (6 lines) by 2 years after randomization compared with a sham treatment

ANTI-VEGF

• Interferon-alpha-2a
• Pegaptanib sodium (Macugen)
• Ranibizumab (Lucentis)
• Bevacizumab (Avastin)
• Afibercept (Eylea)
Anti-VEGF

- Various growth factors are suspected to be involved in the development of this CNV, such as vascular endothelial growth factor (VEGF).

Anti-VEGF

- Anti-VEGF drugs have been shown to reduce the risk of vision loss
- Vision loss still occurred in many treated cases
- Antiangiogenic effect or antipermeability effect?
Interferon-alpha-2a

- Weak inhibitor of angiogenesis
- Commercially available
- When tested in a randomized clinical trial, however, the treatment was found to be of no benefit, and possibly harmful, compared to placebo treatment.

Pegaptanib sodium (Macugen)

• Modified oligonucleotide
• Binds to an isoform of vascular endothelial growth factor (VEGF)
• Injections were given every 6 weeks
• Primary endpoint
  – Proportion of patients losing less than 3 lines of visual acuity by week 54
  – 15% in favor of treatment (70% vs 55%; $P < 0.001$) for the 294 patients receiving pegaptanib 0.3 mg.

Ranibizumab (lucentis)

- A recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use
- Binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A)
- Molecular weight of approximately 48 kilodaltons
Ranibizumab

• Ranibizumab binds to VEGF-A

• Prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells

• Reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.
Ranibizumab Trials

- **MARINA**
  - Efficacy of ranibizumab vs sham treatment for 
  *minimally classic or occult with no classic subfoveal* choroidal neovascular lesions and presumed recent disease progression

- **ANCHOR**
  - Efficacy of ranibizumab vs PDT with verteporfin for *predominantly classic subfoveal* CNV lesions.
Efficacy of ranibizumab vs PDT with verteporfin for predominantly classic subfoveal CNV lesions.

Monthly ranibizumab for 24 months

**ANCHOR- Outcomes**

**12 months**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Verteporfin PDT N=143</th>
<th>Lucentis 0.5mg N=140</th>
<th>Estimated difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of &lt; 15 letters in VA (%)</td>
<td>64.3 %</td>
<td>96.4%</td>
<td>33%</td>
</tr>
<tr>
<td>Gain of ≥ 15 letters in VA (%)</td>
<td>5.6%</td>
<td>40.3%</td>
<td>35%</td>
</tr>
<tr>
<td>Mean change in VA (letters)</td>
<td>-9.5</td>
<td>+11.3</td>
<td>21.1</td>
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## ANCHOR- Outcomes
### 24 months

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<td>Loss of &lt; 15 letters in VA (%)</td>
<td>65.7 %</td>
<td>89.9 %</td>
</tr>
<tr>
<td>Gain of ≥ 15 letters in VA (%)</td>
<td>6.3%</td>
<td>41.0%</td>
</tr>
<tr>
<td>Mean change in VA (letters)</td>
<td>-9.8</td>
<td>+10.7</td>
</tr>
</tbody>
</table>

ANCHOR Outcomes

• PDT outcomes likely were better than the natural course of the disease

• Monthly intravitreal ranibizumab persisted through at least 2 years compared with standard applications of PDT.

MARINA

- Efficacy of ranibizumab vs sham treatment for minimally classic or occult with no classic subfoveal choroidal neovascular lesions and presumed recent disease progression

# Marina outcomes

12 months

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Sham N=238</th>
<th>Lucentis 0.5mg N=240</th>
<th>Estimated difference</th>
</tr>
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<tbody>
<tr>
<td>Loss of &lt; 15 letters in VA (%)</td>
<td>62.2 %</td>
<td>94.6%</td>
<td>32%</td>
</tr>
<tr>
<td>Gain of ≥ 15 letters in VA (%)</td>
<td>5.0%</td>
<td>33.8%</td>
<td>35%</td>
</tr>
<tr>
<td>Mean change in VA (letters)</td>
<td>-10.4</td>
<td>+7.2</td>
<td>17.5</td>
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## Marina outcomes

### 24 months

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<tr>
<td>Loss of &lt; 15 letters in VA (%)</td>
<td>52.9 %</td>
<td>90.0%</td>
<td>33%</td>
</tr>
<tr>
<td>Gain of ≥ 15 letters in VA (%)</td>
<td>4.0%</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>Mean change in VA (letters)</td>
<td>-14.9</td>
<td>+6.6</td>
<td>21.4</td>
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Bevacizumab (Avastin)

• AVASTIN® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

• Molecular weight of approximately 149 kilodaltons.
Bevacizumab (Avastin)

- Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells.
Comparison of Age-related Macular Degeneration Treatments Trial (CATT)

• Designed to answer two questions
CATT Question 1

• Does bevacizumab (Avastin) injected every 4 weeks provide visual acuity results which are equivalent (noninferior) to ranibizumab (Lucentis) injected every 4 weeks with an acceptable safety profile?
CATT Question 2

- Does either bevacizumab or ranibizumab when provided as needed result in visual acuity outcomes equivalent to those following ranibizumab provided every 4 weeks?
CATT Results

• First year

• Answer 1
  – Visual acuity outcomes when using bevacizumab every 4 weeks were equivalent (not inferior) to those when using ranibizumab every 4 weeks?
CATT Results

• First year
• Answer 2
  – Visual acuity outcomes when using ranibizumab as needed, based on examinations every 4 weeks, were equivalent to those when ranibizumab was given every 4 weeks
CATT Results

• First year

• Answer 2
  – Visual acuity outcomes when bevacizumab as needed was compared with ranibizumab every 4 weeks were inconclusive.
CATT Results

• Average as needed treatments
  – Ranibizumab - seven treatments in the first year
  – Bevacizumab - eight treatments in first year
CATT

– No difference between ranibizumab and bevacizumab
  • Myocardial infarction
  • Cerebrovascular accidents
  • Endophthalmitis,
CATT

• Systemic serious AE
  – Ranibizumab 19%
  – Bevacizumab 24%

• Systemic serious adverse events was higher in the bevacizumab as-needed group than the bevacizumab every-4-weeks group; and
CATT

- First year average cost of drug per patient

  - Ranibizumab every-4-weeks $23,400
  - Ranibizumab as-needed $13,800
  - Bevacizumab every-4-weeks $595
Aflibercept (Eylea)

• Fusion protein
  – Key domains of human VEGF receptors 1,2 (VEGFR1, VEGFR2)
  – human IgGFc

• Binds VEGF-A and Placental growth factor (PLGF)
  – Prevent their interaction with native VEGF receptors
View 1,2

• Compared monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab.
VIEW 1,2

- Active, subfoveal, choroidal neovascularization (CNV) lesions

- Juxtafoveal lesions with leakage affecting the fovea
VIEW 1,2

• Randomized to
  – Intravitreal aflibercept
    • 0.5 mg monthly
    • 2 mg monthly
    • 2 mg every 2 months after 3 initial monthly doses
    • Ranibizumab 0.5 mg monthly
• Primary end point

  – Noninferiority of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52

  – Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.
View 1,2 Results

- All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab.

- All aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA.

- All aflibercept regimens also produced similar improvements in anatomic measures.

- Ocular and systemic adverse events were similar across treatment groups.
View 1,2 Conclusions

• Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab.
Aflibercept is an effective treatment for AMD

• Every-2-month regimen
  – Potential to reduce
    • Risk from monthly intravitreal injections
    • Burden of monthly monitoring.
Review Questions

• Name the two major categories of Age Related Macular degeneration.

• What are the clinical stages of Age Related Macular Degeneration

• Name the three injectable anti-VEGF medications available for treating Age related macular degeneration