UPDATE ON AMD 2019

Steven Ferrucci, OD, FAAO
Chief, Optometry, Sepulveda VA
Professor, SCCO/MBKU

Introduction

• Exciting time to be interested in AMD
• Many new treatments now available for AMD
  – Years ago, we had nothing at all to offer patients with AMD
• Current Treatments
• Potential Treatments
• New Diagnostic Equipment

Dry AMD

• Currently mainstream treatment for Dry AMD revolves around prevention of progression through vitamins, nutrition and lifestyle changes
  – Rheophoresis, Laser, Aneortave Acetate did not prove effective
• Early detection of conversion from dry to wet may result in better treatment for patients

AREDS 2

• AREDS 2: Enrollment ended June 2008 with ≈4200 patients followed for six years
  – Effect of lutein, zeaxanthin and omega 3 on AMD
  – Effect of eliminating beta carotene on AMD
  – Effect of reducing zinc on AMD
  – Effect of supplements on cataracts
  – Validate the AMD scale from original AREDS
• Results released May 5, 2013

AREDS 2 Formulation

• Vitamin C-500 mg
• Vitamin E-400 iu
• Lutein 10 mg/Zeaxanthin 2 mg
• Zinc 80 mg
• Copper 2 mg
• NO beta Carotene
• NO Omega-3 fatty acids (DHA/EPA)

Available at www.jama.com
### Wet AMD

- Various agents currently being used as intravitreal injection
  - Macugen® (pegaptanib sodium) Dec 2004
  - Lucentis® (ranibizumab) June 2006
  - Avastin® (bevacizumab) Not FDA approved
  - Eylea® (aflibercept) Nov 2011

### Lucentis (ranibizumab)

- Antibody fragment which blocks VEGF activity
  - Less specific than Macugen, so perhaps more efficacious
  - Delivered by intravitreal injection
  - Developed by Genentech
  - FDA Approved June 30, 2006

### Lucentis

- ANCHOR Study (classic CNVM)
  - 2 Year Phase 3 randomized study
  - 94% of pts treated with 0.3 mg had stable or improved vision vs 64% with Visudyne
  - 38% had gain of 15 letters or more
  - Avg acuity gain was 11.3 letters vs 9.5 letters lost with Visudyne at one year
  - 31% had VA of 20/40 or better vs only 3% with Visudyne
- MARINA Study (minimally classic/occult)
  - 95% of treated pts vs 62% of controls had less than 15 letter loss
  - 25% treated vs 4.6% of controls had 3 line gain
  - At 2 yrs, 6.6 letter gain with tx vs 14.9 letters lost without

### Avastin (bevacizumab)

- Drug currently FDA approved for the treatment of metastatic colorectal cancer and certain lung cancers (Genentech)
  - Parent drug of Lucentis. Originally thought to be too large to penetrate retina
- Currently widely used as treatment for CNVM due to its anti-VEGF properties

### Avastin

- First report of intravitreal injection in May 2005
- First case reports published in July 2005
- Within 6 months, global acceptance and widespread clinical use
  - despite lack of large scale studies regarding efficacy, safety and dosing
Avastin

• Major advantage is COST
  – $15-$50 per 0.3 ml injection
  – 1/40 cost of Lucentis
  – Approx $1k for Macugen/$2.5K for Lucentis
• Issue is there are no large prospective study to judge its efficacy and safety
  – Systemic concern is thrombotic events
    • Amount used in vitreous is 300-400 fold lower than that administered IV
• Some controversy remains but continues to be used widely

Eylea (aflibercept)

View 1

– 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
– 7.9 letter mean improvement of vision (vs. 8.1 with Lucentis monthly)

Eylea

View 2

– 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
– 8.9 letter mean improvement of vision (vs. 9.4 with Lucentis monthly)

Eylea

• Cost: Eylea ≈ $1850/injection, with injection every 2 months
  – Therefore 1/2 of Lucentis monthly
• Second year study will evaluate use PRN

Avastin vs. Lucentis

What is the Treatment of Choice?

• Complications of Age-Related Macular Degeneration Treatment Trial (CATT)
  – NEI/NIH sponsored trial
  – First year results released May 1, 2011 NEJM
• 1208 patients randomized
  – Lucentis with 4 week dosing
  – Avastin with 4 week dosing
  – Lucentis with variable dosing (PRN)
  – Avastin with variable dosing (PRN)

CATT: 1 yr results

• Equivalent effects on visual acuity with same administration
  – Lucentis monthly 8.5 letters gained
  – Avastin monthly 8.0 letters gained
  – Lucentis PRN 6.8 letters gained
  – Avastin PRN 5.9 letters gained
CATT: 1 yr summary

- Vision with Lucentis vs. Avastin relatively equal over course of first year
  - Some evidence of more effect with Lucentis on anatomical structure, i.e. more decrease in RT on OCT, but did NOT correlate with improved visual function
  - Some hint that less systemic events with Lucentis
  - HUGE cost differential
    - Avastin wins most of the time, with select cases benefiting from Lucentis

CATT: 1 yr results

- Average cost for first year treatment:
  - $23,400 for Lucentis monthly
  - $13,800 for Lucentis PRN
  - $595 for Avastin monthly
  - $385 for Avastin PRN

CATT 2 yr Results

- At end of 2 years, both had similar effects on vision when the dosing regimen was the same
  - Mean gain in acuity, proportion gaining or losing 3 lines, % better than 20/40 all similar
  - Mean gain slightly better for monthly vs. as needed, 2.4 letters
  - Rates of death and thrombotic events similar
  - Pts with serious systemic adverse effects higher with Avastin (39.9% vs. 32.7%)

Other studies

- Multiple other comparative studies have confirmed no clinically significant differences between Avastin and Lucentis
  - CATT (US)
  - IVAN (Great Britain)
  - MANTA (Austria)
  - GEFAL (France)
  - BRAMD (Netherlands)
  - LUCAS (Norway)

Seven-Up study

**Seven-Up Study**

Seven-Up Outcomes in Ranibizumab-Treatments in ANCHOR, MARINA, and RIZON

decenter Cohort Study (SEVEN-UP)
CATT 5 yr Results

- ARVO 2016: 647 patients 328 Lucentis, 319 Avastin
- 5.5 years follow up on average
  - 25 total Visits or ≈4.55/year
- 50% had VA > 20/40
- 20% <20/200
- 10% 20/20
  - Loss of 3 letters from baseline
  - Loss of 11 letters from 2 year study endpoint
- Before VEGF: only 10% > 20/40

Potential Therapies

- Currently, there are ≈ 1404 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (March 2018)
- More than:
  - glaucoma
  - dry eye
  - diabetic eye disease
- Exciting time to be involved, with many possible therapies that may prove useful for our AMD patients

FoVista (pegpleranib)

- Anti-PDGF agent
- Theory is that when used in conjunction with anti-VEGF agents, will have a better effect due to synergistic effect
- Ophthotech
  - Phase 1/2b studies promising

FoVista

- Initial phase 1 trial to show safety
  - 59% had improvement of three lines or more
- Phase 2b study: 449 patients
  - FoVista/Lucentis combination gained 10.6 letters at 24 weeks, vs. 6.5 with Lucentis alone
  - 62% additional benefit
  - First study to show results BETTER THAN Lucentis
- Phase 3: FoVista 1.5 mg with anti-VEGF vs anti-VEGF monotherapy underway

FoVista: Update

- Dec 2016, Phase 3: 1248 pts with wet AMD
  - FoVista plus Lucentis: mean gain of 10.24 letters at 1 year
  - Lucentis only: mean gain of 10.01
  - Difference of 0.23 letters
  - 24.2% gained >20 letters with combo
  - 22.1% gained >20 letters with Lucentis alone
  - 12.1% lost 5 letters or more with combo
  - 11.2% lost 5 letters with Lucentis alone
  - 13.5% VA of 20/25 or better with combo
  - 13.9% VA of 20/25 or better with Lucentis

STOCK DECREASED 85% OVERNIGHT!!

Rinucumab

- Another PDGF from Regeneron
- CAPELLA study
  - Eylea plus rinucumab vs. Eylea alone for 12 weeks
  - Combo gained 5.8 letters, Eylea 7.5 letters
  - Failed to meet endpoint
  - Will continue study for one additional year
**Lampalizumab**

- Intravitreal injection for GA (Roche)
- MAHALO study
  - 20% reduction in GA lesion progression over 18 mos who monthly injections
  - Subset of pts with CFI injection had 44% reduction
- Phase III: 986 patients currently underway
- CHROMA, SPECTRI studies
  - First results released September
  - Did not show a positive effect vs. no treatment on lesion size

**Brolucizumab (RTH258)**

- Previously ESBA 1008
- Single chain antibody fragment (scFv)
- Smaller than current agents, yet potentially longer duration
- Phase II study: 194 patients
  - ESBA 1008 0.5, 3, 4.5, or 6 mg vs. 0.5 mg Lucentis
  - At 1 mos, mean VA improvement
    - 6 mg ESBA 1008: 10.4 letters
    - 0.5 mg Lucentis: 6.5 letters

**Brolucizumab (RTH258)**

- HARRIER and HAWK (phase 3 studies)
  - 6 or 3 mg of RTH258 vs. 2 mg Eylea in ~1800 patients
  - Met primary endpoint at 48 weeks of non-inferiority in mean BCVA vs. Eylea
  - ~55% remained on q 12 weeks injection schedule
  - Overall ocular and non-ocular adverse events were comparable to Eylea
  - “These results demonstrate RTH258 has potential to reduce injection burden while providing excellent visual outcomes”

**Replenish®**

- Replenish® drug delivery pump by Alcon/Novartis
- Fully programmable, refillable pump
- Rechargeable to support chronic use
- Applicable to back of eye disorders
- May prove alternative to injections
- Looking at with ESBA 1008/RTH 258 Proof of concept

**LADDER Study**

- Genentech looking at a Rigid Port Delivery System (RPDS)
- Placed through a scleral incision
- Would release a constant influx of meds (Lucentis) rather than serial anti-VEGF injections
- Refillable every 4-6 mos
- Currently in Stage II

**PAN-9080**

- Pan Optica Biotech
- Topical anti-VEGF agent
- Phase 1/2 study
  - Positive response in 45-50% of 20 pts at 8 weeks
    - Decreased Vascular leakage
    - Change in lesion morphology
    - Change in Acuity
    - AE: SPK
- Also looking at role in DR and VO
- Data expected early 2019
**Sunutib (G-102)**

- Gray Burg Vision
- Encapsulated injectable sustained release formulation of SUTENT (Pfizer)
  - FDA approved 2006 for oral tx of advanced renal cell carcinoma, GI stromal tumors, and pancreatic non-endocrine tumors
- Has Anti-VEGF, Anti PDGF, stem cell growth factors and other modes of action
- Injected once per 6 mos
  - G-103: Yearly injection
- Animal studies currently, with human studies planned

**OPT-302**

- OPHTHEA: Australian Biotech company
- Blocks VEGF-C/D
- Phase 2b studies in US and Europe (351 pts)
  - Lucentis plus two doses of OPT-302 for WET AMD
    - Primary Endpoint: change in acuity at 24 weeks
    - Secondary Endpoints
      - Decreased retinal thickness
      - 96 pts with > 15 letter gain in acuity
      - Ocular and non-ocular adverse events

**ICON-1**

- Iconic Therapeutics
- Tissue factor TF inhibitor for WET AMD
  - Interferes with TFs ability to drive angiogenesis and inflammation
- EMERGE STUDY: 88 pts
  - Well tolerated
  - In conjunction with anti-VEGF
    - Reduced CNVM lesion size
    - Removed fluid from retina
  - Starting Phase 2 studies

**High Dose Atorvastatin**

- 26 pts with AMD and large, multiple soft drusen
- High dose 80 mg atorvastatin (generic lipitor)
  - Typically 10-20 mg/day
- At 12 mos, 23 completed trial
  - Regression of drusen and acuity gain of 3.3 letters in 10/23
  - None progressed to wet AMD

**Stem Cells**

<table>
<thead>
<tr>
<th>Investigational Protocol</th>
<th>Stem Cell Source</th>
<th>Gene Amplification/Gene Silencing</th>
<th>Tissue Type</th>
<th>Characteristics</th>
<th>Clinical Trial</th>
<th>Status</th>
<th>Length</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMM-01</td>
<td>Bone Marrow</td>
<td>AAV2.sFLT01</td>
<td>Bone</td>
<td>Reduced CNVM lesion size</td>
<td>Project 1</td>
<td>Closed</td>
<td>2 months</td>
<td>15</td>
</tr>
<tr>
<td>BMM-20</td>
<td>Bone Marrow</td>
<td>AAV2.sFLT01</td>
<td>Bone</td>
<td>Reduced CNVM lesion size</td>
<td>Project 2</td>
<td>Closed</td>
<td>2 months</td>
<td>15</td>
</tr>
<tr>
<td>MKO-25</td>
<td>Kidney</td>
<td>AAV2.sFLT01</td>
<td>Kidney</td>
<td>Reduced CNVM lesion size</td>
<td>Project 5</td>
<td>Closed</td>
<td>2 months</td>
<td>15</td>
</tr>
<tr>
<td>MKO-35</td>
<td>Kidney</td>
<td>AAV2.sFLT01</td>
<td>Kidney</td>
<td>Reduced CNVM lesion size</td>
<td>Project 6</td>
<td>Closed</td>
<td>2 months</td>
<td>15</td>
</tr>
<tr>
<td>PFO-005000000</td>
<td>Fat Pre-adipose</td>
<td>AAV2.sFLT01</td>
<td>Fat</td>
<td>Reduced CNVM lesion size</td>
<td>MKO-35</td>
<td>Closed</td>
<td>2 months</td>
<td>15</td>
</tr>
</tbody>
</table>

If defective gene responsible for abnormal VEGF expression can be localized, perhaps a replacement, or fixer gene, can be injected into the eye ONE TIME!

- Genzyme
- AAV2.sFLT01
- Avalanche Biotechnologies
- AVA-101
- Oxford BioMedica
- RetinoStat
- For Sight Labs
- NeuroTech
**Brimonidine®**

- Glaucoma medication by Allergan
- Long suspected to have neuro-protective properties
  - New studies point at retinal neuroprotection in animals
- BEACON STUDY
  - Evaluating an intravitreal insert for GA
  - 2016 AAO subspecialty day
    - 132ug: 19% reduced rate of regression
    - 265ug: 28%

**APL-2**

- Apellis Pharmaceuticals
- Intravitreal Complement factor C inhibitor for GA
- FILLY Trial: Phase 2 showed decreased rate of lesion progression over 12 mos in monthly and every other month administration
  - Monthly: 26%
  - Ever other: 20%
- Phase 3 to start soon

**MacuLogix’s AdaptDx**

- Dark adaptation is a sensitive marker for early AMD
- The AdaptDx measures dark adaptation
- A rapid test of dark adaptation using the AdaptDx has been found to have a 90% sensitivity for detecting dark adaptation impairment associated with AMD
- Decreased dark adaptation may precede clinical findings of AMD
- Dark adaptation is more sensitive than other tests such as Snellen acuity, contrast sensitivity, or visual fields which are about 25% sensitive.

**AdaptDx Study at VA**

- Tested whether the AdaptDx could detect AMD in a typical VA clinical setting
- Rapid test run on 19 AMD patients (AREDS stage: 1 to 3)
- 18 of 19 patients failed to dark adapt before the maximum test time of 6.5 minutes. The diagnostic test sensitivity was 94.7%
- The AdaptDx exhibited similar sensitivity in a working VA clinic compared with a multi-site clinical study
- Next step is to use the AdaptDx to find patients with undiagnosed AMD or subclinical AMD

**AdaptDx Advantages**

- No preadaptation required
- Protocols as rapid as 5 minutes
- Low patient burden
- Easy to operate
- CPT 92284 ($64 avg.)
- FDA 510K cleared (K100954)

**Foresee Home**

- Trend analysis
- High definition scans
- Customized treatment plans
AREDS 2 home study

- 1520 pt with at least one large drusen and VA 20/60 better
  - 763 with home monitoring, 51 CNVM detected
  - 757 standard monitoring, 31 CNVM detected
    - 4 letters lost with device vs. 9 without
    - 94% had better than 2040 with device vs. 87% without

My Vision Track (mVT®)

- An app to detect early vision problems in patients with AMD and DM, leading to sooner assessments and better vision retention
- FDA cleared
- 98% effective rate in detecting changes

CONCLUSION

- Exciting time to be interested in AMD
- New treatments on horizon that may be beneficial to our patients
- New advances in diagnosis and detection are paramount
  - On study determined 25% of pts deemed normal on dilated retinal exam by eye care physician had characteristics of AMD on photographic review