Retinovascular disease and developing therapies

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Age-related macular degeneration

AMD
ARMD

Contents

Age related macular degeneration
Diabetic eye disease
Vein occlusion
Risk factors for Advanced AMD

- Age
- Family history
- Complement factor H mutation
- Smoking
- Elevated CRP
- UV exposure?

Intermediate AMD

Category 3 – Extensive Intermediate or Large Drusen (>125 microns)

Advanced AMD

Category 4: Neovascular AMD or Central Geographic Atrophy in 1 eye

Age-Related Eye Disease Study (AREDS)

Randomized Participants

- Placebo N=1,483
- Antioxidant N=1,482
- Zinc N=904
- Antioxidant & Zinc N=888

Results published 2001
**Rate to Advanced AMD**

**AMD Categories 3 and 4 by Treatment Group**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Antioxidants</th>
<th>Zinc</th>
<th>Antioxidants + Zinc</th>
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<tbody>
<tr>
<td>Estimated Probability</td>
<td>0%</td>
<td>10%</td>
<td>20%</td>
<td>28%</td>
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</tbody>
</table>

P vs. A+Z – p<0.01
P vs. Z – p<0.01

**AMD Trial - Summary**

**Estimate of Risk Reduction**

Developing Any Advanced AMD, Neovascular or Geographic Atrophic AMD

- Antioxidants: 17%
- Zinc: 21%
- Antioxidants & Zinc: 25%

**AREDS Formulation**

**Antioxidants – Daily Oral Dose**

- Vitamin C – 500 mg
- Vitamin E – 400 IU
- Beta-carotene – 15 mg

- Zinc - 80 mg zinc oxide
- Copper - 2 mg cupric oxide

**AMD Grading and Predictive Scale**

*Archives Ophthalmology 2005; 123: 1570*

**What if you do get wet AMD?**

Joan Miller MD “Paradigm shifts”

- Dark ages: Thermal laser in the 1980s and 1990s
- Middle Ages: PDT 2000-2006
- Renaissance: anti-VEGF therapy 2006 onward

**Vascular endothelial growth factor**

Chromosome 6p21.3

Hypoxia upregulates transcription
Vascular endothelial growth factor
VEGF121 is soluble.
VEGF189 is bound to extracellular matrix.
VEGF 165 is intermediate.
VEGF189 may reside in ECM as a reservoir.
Proteases released during angiogenesis may liberate VEGF.

VEGF
Induces endothelial cell intracellular signaling, migration, angiogenesis, and vascular permeability

VEGF Receptor 1 and VEGF Receptor 2 mediate intracellular phosphorylation

VEGF roles
Anti-apoptosis signaling in endothelial cells
Neural retina development
Leukocyte adherence
Differentiation and protection of cortical neurons, astrocytes, and Schwann cells
Ranibizumab (Lucentis)
Blocks VEGF121, VEGF145, VEGF165, VEGF183, VEGF189, and VEGF206

48 kDa molecule

14 times the affinity for VEGF compared to Avastin
Lucentis vs PDT: classic CNV

Lucentis: monthly dosing for 3 months, then every 3 month dosing

PRONTO study: OCT guided dosing

Average gain of 9 letters

5.6 injections over one year

35% had a 3 line gain

Injection free interval of 4.5 months
Arterial thromboembolic events (ATEs)

- Stroke
- Heart attack
- Blood clots

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<thead>
<tr>
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<th>Control arm</th>
<th>Lucentis arm</th>
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<tbody>
<tr>
<td>ATEs</td>
<td>1.1% (5/441)</td>
<td>2.1% (18/874)</td>
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MARINA Two year data

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<th>Control arm</th>
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<tr>
<td>ATEs</td>
<td>3.2% (7/216)</td>
<td>3.0% (14/466)</td>
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</table>

ANCHOR and MARINA One year data

Lucentis clinical trials

SAILOR extension trial--followup 230 days

1.2% incidence of CVA in 0.5 mg group versus 0.3% in the 0.3 mg group (p=0.02). Patients with a history of prior stroke are at higher risk. No difference in MI or vascular death.
Ranibizumab phase I FVF1770g
10 subjects received a single intravitreal dose 0.3 to 1 mg.
Serum concentrations were less than 3 ng/mL, less than the 11-27 ng/mL that is hypothesized to have a significant effect on physiologic VEGF-induced endothelial cell proliferation.
The steady state serum concentration with monthly dosing at 0.5 mg was 0.22 ng/mL.

Lucentis serum pharmacoekinetics
At a serum concentration of 0.8 to 3 ng/mL, 12% of serum VEGF will be bound.
At 13 days after injection, 1% of serum VEGF will be bound.

Pharmacokinetics of Avastin
Bakri et al; Ophthalmology May 2007
Intravitreal injection of 1.25 mg in rabbits.
Vitreous half life=4.3 days.
Peak serum concentration of 3.3 ug/mL at 8 days, falling below 1 ug/mL at 29 days.
Serum half life 6.86 days.

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<tr>
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<th>Avastin Rabbit model</th>
<th>Avastin Monkey model</th>
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<tbody>
<tr>
<td>Peak vitreous concentration</td>
<td>400 ug/mL</td>
<td>169 ug/mL</td>
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<tr>
<td>Time to peak vitreous concentration</td>
<td>1 day</td>
<td>6 hours</td>
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<tr>
<td>Vitreous half life</td>
<td>4.3 days</td>
<td>2.6 days</td>
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<tr>
<td>Peak serum concentration</td>
<td>3.33 ug/mL (0.8% of vitreous C max)</td>
<td>150 ng/mL (0.08% of vitreous C max)</td>
</tr>
<tr>
<td>Time to peak serum concentration</td>
<td>8 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Serum half life</td>
<td>6.86 days</td>
<td>3.5 days</td>
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Avastin
150 kDa
Whole antibody

7113 injections in 5228 patients from November 2005 to April 2006
Potential drug-related systemic AEs
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<thead>
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<tr>
<td>Blood pressure increase</td>
<td>15 (0.21)</td>
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<tr>
<td>Deep venous thrombosis</td>
<td>1 (0.01)</td>
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<tr>
<td>Transient ischaemic attack</td>
<td>1 (0.01)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5 (0.07)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.03)</td>
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Avastin internet registry
Future wet AMD developments

VEGF Trap
VEGF Receptor fused to an IgG Fc
Phase III trial VEGF trap vs. Lucentis
Regeneron Pharmaceuticals/Bayer

Combination treatments
VERITAS trial
PDT with either intravitreal Macugen or triamcinolone
Disappointing results
Search for durability

Small interfering RNA
Blocks translation of VEGF RNA into VEGF protein
Cand5/Bevasiranib from OPKO Health (phase III trial COBALT: 3 Lucentis and then Bevasiranib every 8 or 12 weeks)
AGN211745 from Allergan/Sirna Therapeutics (phase II)

Lucentis + PDT
• DENALI
• MONTBLANC
• Various small “reduced fluence” PDT trials in combination with anti-VEGF agent and steroid

Neovista
• CABERNET trial phase III
CATT
Lucentis vs. Avastin
NIH/NEI sponsored trial
Dan Martin, MD; Emory University

Diabetic retinopathy

Panretinal photocoagulation
Focal laser photocoagulation

Anti VEGF agents and macular edema

Global Diabetic retinopathy project group
Ophthalmology 2003; 110: 1677

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<th>Focal laser Photocoagulation</th>
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Table 2: Diabetic Retinopathy Disease Severity Scale

- Diabetic retinopathy
- Macular edema
- Vascular leakage
- Neovascularization
- Cataract

Findings: Observable on Diabetic Ophthalmoscopes

- Mild diabetic macular edema: Some retinal thickness or hard exudates in peripapillary but not the center of the macula
- Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center
- Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula

Results: 1 line gain; 68 micron thickness reduction at 36 weeks

Problems: No comparison to laser, and short followup.

Evolving non-laser therapies for diabetic retinopathy

Macugen for DME
Ophthalmology 2005 112: 1747

Randomized controlled trial, with a sham injection control arm

Injections at 0, 6 and 12 weeks

Results: 1 line gain; 68 micron thickness reduction at 36 weeks

Problems: No comparison to laser, and short followup.

Avastin for diabetic macular edema
Pan-American Collaborative Retina Study Group
Retrospective case series
Small VA and retinal thickness benefit at 6 months followup
Avastin for diabetic macular edema
*Ophthalmology* October 2007

DRCR.net phase II study
5 treatment arms

At 12 and 24 week followup, no difference between Avastin and laser

No synergistic effect

Steroids for macular edema associated with diabetes
www.DCRR.net

*Intravitreal triamcinolone versus laser randomized trial: 689 patients*

Lucentis for DME

Phase I trials: encouraging short term visual acuity and retinal thickness results

Phase 2 trial (READ-2) with 18 month followup, results in 2009.
3 arms: laser alone, Lucentis alone, laser + Lucentis

Long term delivery solutions for macular edema

Retisert
Medidur (FAME trial, phase III)
Posurdex

Steroids for macular edema associated with diabetes


Subtenons steroid injections combined with focal laser.

No additional benefit with steroids.

Anti-VEGF therapy and proliferative diabetic disease
Diabetic retinopathy

- Laser is still a mainstay of therapy.

- With good compliance, very few patients go blind upon long term followup (Ophthalmology 2003; 110: 1683).

- Intravitreal anti-VEGF therapy and/or steroid may be useful in special situations.
Vein occlusions: customize approach

Steroids for macular edema associated with vein occlusion

Case series: short term improvements in vision and retinal thickening, but long term results disappointing.

SCORE study
Vein occlusions

Laser is still a mainstay.

May combine with subtenons or intravitreal steroids.

Be careful with anti-VEGF therapy in vein occlusion macular edema: rebound phenomenon *Retina* 2007; 27: 426

Bottom line on the retinovascular front AMD: lots of good news.

Diabetes and vein occlusion: There’s not much new that is evidence based. Avastin for PDR/NVG short term relief can be useful.

Where AREDS comes from: 3rd floor