Kapusta AMD Part 1

Management of Neovascular AMD

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McGill
FINANCIAL DISCLOSURES

Consulting honoraria - Bayer, Novartis, Alcon
Advisory panel - Artic Dx

AGE-RELATED MACULAR DEGENERATION is a leading cause of irreversible blindness among people who are 50 years of age or older in the developed world. The neovascular form of the disease usually causes severe vision loss and is characterized by the abnormal growth of blood vessels under the retina.
Background

Search Results: 25174

Published in the past 10 years:

Search Results: 15528

62.7%

“Anti-VEGF Era”

AMD Management: Teaching points

① Drug of choice
② Treatment Regimen
③ Signs for re-treatment
If Avastin, Lucentis, and Eylea cost the same, which would you use for new-onset wet AMD?

5. If Avastin (bevacizumab, Genentech, Inc, South San Francisco, CA), Lucentis (ranibizumab, Genentech, Inc), and Eylea (afibercept, Regeneron Pharmaceuticals, Inc, Tarrytown, NY) were the same cost for each patient, which drug would you use primarily for treating new-onset age-related macular degeneration (AMD)?
**Visual outcomes** in major treatment trials of neovascular AMD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration of follow-up (years)</th>
<th>Mean change in visual acuity in treatment group (letters)</th>
<th>Mean change in visual acuity in control group (letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS (extravascular) Laser</td>
<td>5</td>
<td>-25</td>
<td>-35</td>
</tr>
<tr>
<td>MPS (subfoveal) Laser</td>
<td>5</td>
<td>-25</td>
<td>-30</td>
</tr>
<tr>
<td>MPS (subfoveal) Laser</td>
<td>4</td>
<td>-20</td>
<td>-25</td>
</tr>
<tr>
<td>PDT</td>
<td>2</td>
<td>-3</td>
<td>-9</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>2</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>2</td>
<td>-10</td>
<td>-15</td>
</tr>
<tr>
<td>ANCHOR</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>Photodynamic therapy</td>
<td>2</td>
</tr>
<tr>
<td>MARINA</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>Placebo</td>
<td>2</td>
</tr>
<tr>
<td>PROVE</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>SUSTAIN</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>SAILOR</td>
<td>Ranibizumab 0.5 mg monthly for 3 months then as needed</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>CATT</td>
<td>Bevacizumab 1.25 mg monthly</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>1</td>
</tr>
<tr>
<td>VIBRANT 1</td>
<td>Aflibercept 2 mg twice-monthly</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>1</td>
</tr>
<tr>
<td>VIBRANT 2</td>
<td>Aflibercept 2 mg twice-monthly</td>
<td>Ranibizumab 0.5 mg monthly</td>
<td>1</td>
</tr>
</tbody>
</table>

Table: Visual outcomes in major treatment trials of age-related macular degeneration


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**Anti-VEGF therapy**

- Class of drugs that has become firmly established as the **standard of care**
- **Pegaptanib** (Macugen, Pfizer)
  - A small oligonucleotide molecule that specifically binds the VEGF-165 isoform.
  - **First drug** to obtain US FDA approval for AMD in **2004**.
  - More patients with visual stabilization than placebo.
- **Ranibizumab** (Lucentis, Genentech/Novartis)
  - Antibody fragment that binds **all VEGF isoforms**
  - **Second anti-VEGF drug approved by the FDA in 2006**.
  - Landmark clinical trials showed not only visual stabilization but, for the first time, **substantial visual gains** as well.
Visual acuity changes with ranibizumab. Mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) letters through:

- **ANCHOR, MARINA**: 12-month follow-up with 0.5 mg ranibizumab for monthly injections
- **PIER**: A Study of rhuFAB V2 (Ranibizumab) in Subjects with Subfoveal CNV Secondary to AMD.
- **PRONTO**: Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intravitreal Ranibizumab (Lucentis)
- **SAILOR**: A Study to Evaluate Ranibizumab in Subjects With CNV Secondary to AMD
- **HORIZON**: An Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects with CNV Secondary to AMD or Macular Edema Secondary to RVO

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**Anti-VEGF therapy**

- **Bevacizumab (Avastin, Genentech)**
  - Commonly used as an alternative off-label treatment since 2005.
  - Full-length antibody that binds all VEGF isoforms.
  - Originally developed and approved for systemic malignancies.
  - Bevacizumab is the most commonly used anti-VEGF drug in the USA.

- **CATT trial** showed that bevacizumab and ranibizumab had equivalent efficacy: bevacizumab given monthly was non-inferior to ranibizumab given monthly or PRN:
  - mean 8.0 letters gained with bevacizumab
  - mean 8.5 letters gained with ranibizumab
Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group

Abstract

BACKGROUND—Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS—In this randomized, single-masked, noninferiority trial, secondarily assigned 108 patients with neovascular AMD were randomized to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 7 letters on the ETDRS chart.

RESULTS—Ranibizumab administered monthly was equivalent to ranibizumab administered monthly, with 0.2 and 0.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 0.9 and 0.3 letters gained, respectively. Ranibizumab as needed was noninferior to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was not powered. Differences were greatest in the monthly-ranibizumab group (96.3%) than in the other groups (15% or 100%) and were similar for patients not receiving ranibizumab (94.5% for both groups).

CONCLUSIONS—Although 0.2 letters of visual acuity were gained on average among patients randomized to the same injection schedule, ranibizumab given as needed with a monthly evaluation had effects on visual acuity that were similar in those of ranibizumab-administered monthly. Differences in rates of adverse events require further study (Funded by the National Eye Institute, ClinicalTrials.gov number: NCT00096827).

Change in Visual-Acuity Score from Baseline to 1 Year

![Graph showing change in visual acuity score from baseline to 1 year for ranibizumab monthly, bevacizumab monthly, and as needed.](image-url)
Change in Visual-Acuity Score from Baseline to 1 Year

Findings on Optical Coherence Tomography
### Anti-VEGF therapy

- **Aflibercept (Eylea, VEGF Trap-Eye, Regeneron/Bayer)**
  - **Recombinant fusion protein** consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration.
  - **FDA approved** for neovascular AMD in 2011.
  - The **binding affinity** of aflibercept is higher than that of ranibizumab and bevacizumab.
  - Aflibercept also binds to **placental growth factor (PIGF)** present on endothelial cells and leukocytes.

### Table: Aflibercept (VEGF Trap-Eye, Regeneron/Bayer)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Molecular weight</th>
<th>Mechanism of action</th>
<th>Binding affinity to VEGF-A (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>Fusion protein domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused to human IgG1 Fc</td>
<td>Binds to all isoforms of VEGF-A, VEGF-B, and PIGF</td>
<td>0.5 pM</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Monoclonal IgG antibody fragment (Fab)</td>
<td>Binds to all isoforms of VEGF-A,B</td>
<td>66 pM</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal IgG antibody</td>
<td>Binds to all isoforms of VEGF-A,B</td>
<td>38 pM</td>
</tr>
</tbody>
</table>

*Abbreviations: VEGF, vascular endothelial growth factor; IgG, immunoglobulin G.*
Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

Jeffrey S. Heier, MD; David M. Brown, MD; Viera Chong, MD; Jean-François Kowalchyk, MD; Pavel K. Kaiser, MD; Quan Dong Nguyen, MD; Bernd Krickl, MD; Allen Hs, MD; Takehito Oyama, MD; George D. Younge, MD; PKBD; Zafar Sultani, MD; Robert Vodovotz, MD; Alyson J. Berkov, MD, PhD; Yuko Saiki, PhD; Majj Aulrabe, MD; Georg Greve, MD; Bernd Sonnewasser, MD; Harriet S. Roper, MD; MD; and Christian Strader, MD.

**Objective:** Two similarly designed, phase-3 studies (VIEW 1, VIEW 2) of intravitreal aflibercept (VEGF Trap-Eye) in neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye), Ranibizumab, and Ranibizumab.

- Aflibercept dosed **monthly or every 2 months** after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab.
- Effective treatment for AMD, with the every-2-month regimen.
- Reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis.
Mean change from baseline in central retinal thickness

How are they different?

#1 - FDA approval

While Lucentis and Eylea have been FDA-approved for use in the eye, Genentech, the company that manufactures Avastin, as well as Lucentis, has not sought FDA approval for Avastin to be used as treatment of wet AMD.

However, Avastin was FDA-approved as a treatment for colon cancer in February 2004, and since then has been used by ophthalmologists to treat wet AMD "off-label".
How are they different?

#2 - Cost

Avastin, at approximately $50 per average treatment, is significantly less expensive for the patients / health care system than the alternatives (~$1,800 for Eylea and ~$2,000 for Lucentis).

How are they different?

#3 - Risks

Numerous studies have concluded that there are minimal differences in risk between the three drugs.

A concern is that there is a greater possibility of infection with Avastin due to potential contamination when the drug is being repackaged into smaller doses for the eye.
#4 - Packaging and accessibility

Since Lucentis and Eylea are FDA approved for use in the eye, they are manufactured and delivered to ophthalmologists as eye injectables, usually stored in the ophthalmologist’s office and available for use whenever they are needed.

Avastin, in contrast, is a repackaged drug. It is shipped from the manufacturer to a special pharmacy that repackages it into smaller doses for the eye and then delivers it to doctors’ offices.
Laser photocoagulation therapy and verteporfin PDT have shown benefits compared with the natural course in selected subtypes and stages of neovascular AMD.

Application of photocoagulation or PDT for subretinal new vessels is likely to be considered in current clinical practice in less common conditions:

- Peripapillary CNV
- Any extrafoveal CNV
- Extrafoveal CNV in pregnant women in whom neither PDT nor intravitreal VEGF inhibitors have been shown to be safe.

Polypoidal Choroidal Vasculopathy

EVEREST trial: controlled study has been performed to prove the efficacy and safety of Ranibizumab Vs PDT or PDT plus Ranibizumab

- 61 PCV patients of Asian ethnicity from 5 countries.
- 6 months EVEREST study results suggests that in a majority of patients, Visudyne® therapy, with or without Lucentis®, may lead to complete regression of the polyps that can cause vision loss in patients with PCV.

A complete polyp regression was achieved:
- 77.5% of patients who received Visudyne® – Lucentis®
- 71.4% of Visudyne® monotherapy
- 26.0% of patients in the Lucentis® monotherapy group (p=0.0018 for combination, p=0.0037 for Visudyne® vs. Lucentis®)
- BCVA from baseline to month six improved in average in all combination group achieving the highest gain (+10.9 letters from baseline)
In PCV patients, the visual acuity improvement achieved after 12 months of intravitreal aflibercept did not differ significantly from that achieved using intravitreal ranibizumab. However, aflibercept treatment more often led to polyp regression than did treatment using ranibizumab.

**AMD Management : Teaching points**

① Drug of choice
② Treatment Regimen
③ Signs for re-treatment
② Treatment Regimen

1. Continuous Treatment

- Treating every month or two is effective
- Overtreating some patients
- Costly
- Inconvenient for patients – treatment burden
- Higher risk of geographic atrophy than PRN

* increased rate of GA was documented with monthly use of ranibizumab had new GA lesions after 2 years compared with only 15% of eyes treated in the as-needed arm.
2. PRN Treatment

- Good results the first year
  - **IVAN study:**
    - ranibizumab or bevacizumab given either every month (continuous) or as needed (p.r.n.).
    - The comparison of visual acuity at one year between the two drugs was inconclusive, and visual acuities with continuous and PRN treatment were equivalent
  - **CATT study:**
    - Patients who were given the same treatment regimen for two years, the mean gain in visual acuity was similar for both drugs.
    - The mean gain was greater for monthly than for as-needed treatment.

*Ophthalmology, 2012 July; 119(7): 1388–1398*
- Eyes that switched from monthly to as-needed treatment experienced a greater mean decrease in vision during year two and a lower proportion of eyes had no fluid.

3. Treat and Extend

- Customized or Individualized
- Lower risk of geographic atrophy compared with that observed with continuous monthly treatment
Systematic Review: The study suggests superiority of Treat and Extend regimen to PRN in a 12 month period.

Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration

Charles C. Wykoff, MD, PhD, Daniel E. Croft, BA, David M. Brown, MD, Rui Wang, BA, John F. Payne, MD, Lloyd Clark, MD, Nizar Saleh Abdelfattah, MD, SivVasu R. Sadda, MD

The TREX neovascular AMD management strategy used in this prospective, randomized, controlled trial resulted in visual and anatomic gains comparable with those obtained with monthly dosing.