Kapusta amd part 2
What is your experience during chronic treatment for wet AMD (2 or more years) with anti-VEGF agents?

12. What is your experience during chronic treatment for wet AMD (2 or more years) with anti-VEGF agents?
Vision gains during the first 2 years were not maintained at 5 years

Distribution of visual acuity over time

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al.
4. Other factors

- Monocular status
- Status of the fellow eye and VA
- Patient preference – “Snowbirds”

80 yo Caucasian Female

POH:
- AMD OU
- Exudative AMD OS: Peripapillary net
  - s/p Lucentis - regimen T&E (Montreal & Miami)
  - Injections for 2 years (extended to 14 weeks) - with last one Aug 17, 2015
  - Injections discontinued Nov 2015- too good..
  - Q 3 month then Q 6 months F/U

October 31st, 2016
VA 20/30
OCT dry
Last injection 18 months ago
2 weeks after – Decreased VA

VA OS CF 1 feet
Ho AC, Budde BA, Regillo CD, Weland MF, Van Everen SA, Liu Z, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology.*

5. New Technologies

- **OCT Angiography** – Is it going to change our management??

**OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF TIME COURSE OF CHOROIDAL NEOVASCULARIZATION IN RESPONSE TO ANTI-ANGIOGENIC TREATMENT**

David Huang, MD, PhD; Yali Jia, PhD; Marco Rispoli, MD; Du Tan, PhD; Bruno Lumbroso, MD
① Drug of choice
② Treatment Regimen
③ Signs for re-treatment
③ Signs for re-treatment

Patients receiving Anti-VEGF treatment should be:

- Monitored at regular intervals (Monthly, PRN, T&E).
- Follow-up visits should include examination for new onset of a decrease in vision and new or persistent metamorphopsia
- BCVA tests should be repeated using identical procedures.
- SD-OCT is required if stereoscopic fundus examination reveals clinical signs of retinal edema, detachment of the retinal pigment epithelium (RPE) or hemorrhage.

* OCT-Angiography?

These recommendations are based on the Age-Related Eye Disease Study and HOME study (evidence level I) and levels II/III data for clinical management of early AMD.
While the phase III trials used monthly injections, it was unclear at that time if monthly dosing was the best dosing interval.

Observations made after the earlier phase I/II studies suggested a role for OCT in determining the appropriate dosing interval for each patient.

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**PRN vs Monthly**

<table>
<thead>
<tr>
<th>A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEETA A. LALWANI, PHILIP J. ROSENFELD, ANNE E. FUNG, RANDOLPH DUROVY, STEPHEN MICHELS, WILLIAM FELER, JANET L. DAVIS, HARRY W. FLYNN, JR, AND MARIA ESQUADRO</td>
</tr>
</tbody>
</table>

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**PrONTO Study**

**Retreatment was performed:**

- **During the 1st year** at each monthly visit if any criterion was fulfilled such as:
  - Increase in OCT-CRT of at least $\geq 100 \, \mu m$
  - Loss of 25 letters (ETDRS)
  - Fluid detected by OCT
  - Persistent macular fluid detected by OCT
  - New macular hemorrhage
  - New-onset CNV

- **During the 2nd year,** the retreatment criteria were amended to include retreatment:
  - if any **qualitative increase** in the amount of fluid was detected using OCT.
• Despite small and open-label, this study suggested that flexible OCT-guided retreatment could sustain visual gain with fewer injections, a concept which has since become a popular model in clinical practice, particularly in Europe.

**PrONTO Study - OCT-guided** variable-dosing regimen with Lucentis resulting in VA outcomes comparable with those of the phase III studies with monthly dosing while averaging fewer than half the number of injections over 2 years.

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**PRN vs Monthly**

- **CATT trial**
  - ‘zero tolerance’
  - Radial scanning by Time Domain-OCT was used in the trial and any fluid on OCT.
  - PRN using ranibizumab was considered to be non-inferior
  - **Meta-analysis** combining the data from all the groups, as well as the data from the IVAN study, a similar trial in the UK with different retreatment protocol:
    - dis-continuous was inferior to continuous treatment.
    - As the latter also included data from bevacizumab, the findings might have been different, if ranibizumab had been used alone, were in this analysis.
    - changing to PRNin year 2 lost all the benefit of the monthly treatment from year 1

- **HARBOR study**
  - Confirmed that 0.5 mg of ranibizumab dosed monthly provides optimum results in patients with neovascular AMD.
  - No great disadvantage in using a PRN regimen instead of continued monthly injections.
  - Strict monthly monitoring is provided using **SD-OCT technology**.
Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration

PRN groups were evaluated monthly and re-treated if there was a:

- 5-letter decrease in vision from the previous visit or
- Any evidence of disease activity on SD-OCT (intraretinal fluid, SRF, or PED)

*using Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA).

- Monitor disease activity using SD-OCT, and on a monthly base.
- Concept of a ‘zero tolerance’
- However, persistent intraretinal cysts should be considered signs of irreversible retinal degeneration and should not trigger further retreatment.

These recommendations are based on evidence levels I (CATT, VIEW, HARBOR) and evidence levels...
- **Intraretinal cysts, SRF and RPE detachments** are important signs of activity in the neovascular membrane, independent of CRT.

- **SD-OCT or SS-OCT** are more sensitive for detecting of subtle morphological changes and, thus, permit early treatment of exudative recurrence.
Teaching points

What is the most important factor indicating recurrent wet-AMD disease activity in the maintenance phase?

- Loss of vision: US 3.9%
- Subretinal fluid recurrence: US 48.6%
- Intraretinal fluid recurrence: US 1.5%
- Macular hemorrhage: US 9.9%
- PED development: US 4.2%
- Other: US 2.5%

13. In your opinion, what is the most important factor indicating recurrent disease activity in wet AMD during the maintenance phase?

After how many injections do you consider switching anti-VEGF agents due to inadequate response?

- < 3 injections: US 10.3%
- 3-6 injections: US 77.1%
- 7-12 injections: US 9.5%
- > 12 injections: US 2.2%
- Other: US 0.8%

9. How many injections do you give with an anti-VEGF agent before considering switching to another agent due to inadequate response?
Research Article
A Meta-Analysis of Studies Evaluating Visual and Anatomical Outcomes in Patients with Treatment Resistant Neovascular Age-Related Macular Degeneration following Switching to Treatment with Afibercept

Sophie Seguin-Greenstein,1,2 Sue Lightman,3,4 and Oren Tomkins-Netzer1,4,5

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2Clalit Health Services, Tel Aviv, Israel
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With the introduction of afibercept, eyes with neovascular age-related macular degeneration (AMD) not responding well to injections of ranibizumab or bevacizumab can be switched to treatment with afibercept. We carried out a meta-analysis to analyse all available evidence of visual and anatomical outcomes of eyes with resistant neovascular AMD switched to afibercept at six months. Data from seven retrospective and prospective studies showing a change in corrected visual acuity (CVA) and central retinal thickness (CRT) were included. Weighted mean difference (WMD) and 95% CI were estimated using the random-effects model in meta-analysis. Central retinal thickness (CRT) was defined as the average thickness of the central 3 mm of the inner retina. In a total of 237 patients for whom data were available, median CVA improved by 10 letters from baseline to six months following treatment switch to afibercept (WMD = 8.8, 95% CI: 7.7 to 9.8, p < 0.001, and the effect was more significant in eyes with neovascular AMD and CDRS >0.5. There was a significant improvement in CRT following treatment switch to afibercept (WMD = 3.9, 95% CI: 2.6 to 5.3, p < 0.001). Our meta-analysis indicates that following treatment switch to afibercept patients may have significant improvement in CTAW and improved visual acuity.

Figure 1: PRISMA flow diagram of study selection.
### Table 1: Characteristics of all studies included in the Meta-analysis

| Authors | Year | Country | Study | N in pros | N in con | Methodology | Quality | RCTA | CAT | OVR | Overall
|---------|------|---------|-------|-----------|-----------|-------------|---------|------|-----|-----|---------|
| Kumar [24] | 2003 | USA | Retna | 35       | 35       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Beall [25] | 2003 | USA | Retna | 39       | 39       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Ghadri [26] | 2003 | Italy | Retna | 30       | 30       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Messenger [27] | 2003 | USA | Preg | 26       | 26       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Wicks [28] | 2004 | USA | Preg | 61       | 61       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Cheng [29] | 2004 | Australia | Preg | 58       | 58       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2
| Singh [30] | 2004 | USA | Preg | 28       | 28       | RCB, OCT | 2       | NS   | NS  | NS  | Overall 2

- **Legend**: RCB: Randomized Controlled Trial, OCT: Optical Coherence Tomography
- **Quality**: 1: Strong, 2: Moderate, 3: Weak
- **RCTA**: Retna Central Tap Action
- **CAT**: Central Action Test
- **OVR**: Overall Result

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### Only 3 PROSPECTIVE STUDIES

- **Authors**: Kumar [24], Beall [25], Ghadri [26]
- **N in pros**: 35, 39, 30
- **Methodology**: RCB, OCT
- **Quality**: 2
- **Overall Result**: Overall 2

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### Table 2: Clinical characteristics of all studies included in the Meta-analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mean age (years)</th>
<th>Duration of disease (months)</th>
<th>No. of injections prior to conversion</th>
<th>Time between last anti-VEGF and conversion</th>
<th>Mean time of follow up (months)</th>
<th>Mean number of anti-VEGF injections</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar [24]</td>
<td>79 (range 60-86)</td>
<td>12 (range 6-20)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>6</td>
<td>Loading (100%)</td>
</tr>
<tr>
<td>Beall [25]</td>
<td>79 (range 60-86)</td>
<td>12 (range 6-20)</td>
<td>3.5 (range 1-5)</td>
<td>NS</td>
<td>NS</td>
<td>6</td>
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<td>NS</td>
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<td>6</td>
<td>Loading (100%)</td>
</tr>
<tr>
<td>Wicks [28]</td>
<td>72 (range 55-67)</td>
<td>12 (range 6-20)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>6</td>
<td>Loading (100%)</td>
</tr>
</tbody>
</table>
First systematic meta-analysis evaluating the visual and anatomical outcomes of patients with resistant AMD converted to aflibercept.

Evidence that following switching there is a significant anatomical effect, resulting in CRT thinning.

The VA change was far more modest and while there is evidence to support that aflibercept has a comparable effect to other anti-VEGF agents in maintaining vision, any potential significant benefit should be regarded with caution.

Future results, especially from prospective studies, may offer new insights into the different effects of these agents.

**TAKE HOME MESSAGES**

① **Drug of choice**
Hospital-Private setting-Country
$$
Clinical Scenario (PCV, RAP..)

② **Treatment Regimen**
T&E / PRN
If PRN – monthly follow-up

③ **Follow-up / Re-treatment signs**
SD-OCT / SS-OCT
OCT-A
16. In the context of a patient who has had a recent myocardial infarction (MI) or cerebrovascular accident (CVA) and is receiving regular anti-VEGF treatments in both eyes for active neovascular AMD with evidence of persistent intraretinal and subretinal fluid on spectral-domain OCT (SD-OCT), I would:
How do you manage patients with bilateral wet AMD who have elected anti-VEGF therapy for both eyes?

- Inject both eyes at the same visit: US 56.9% (int 68.6%)
- Inject only 1 eye per visit: US 39.9% (int 43.3%)
- Other: US 3.1% (int 1.3%)

7. Which of the following best describes your management of patients with bilateral wet AMD who have elected anti-VEGF therapy for both eyes? 

n = 1033