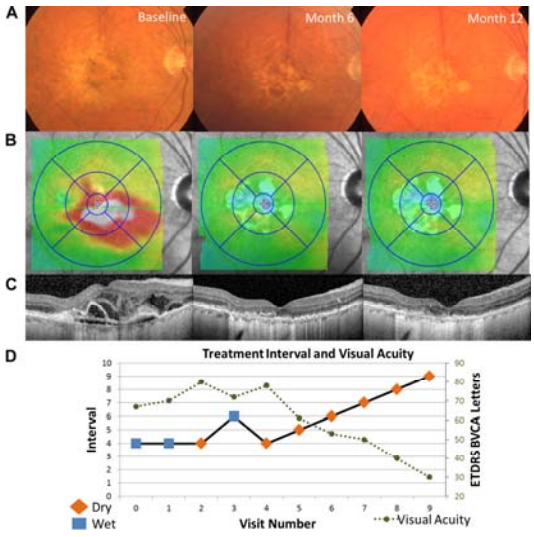
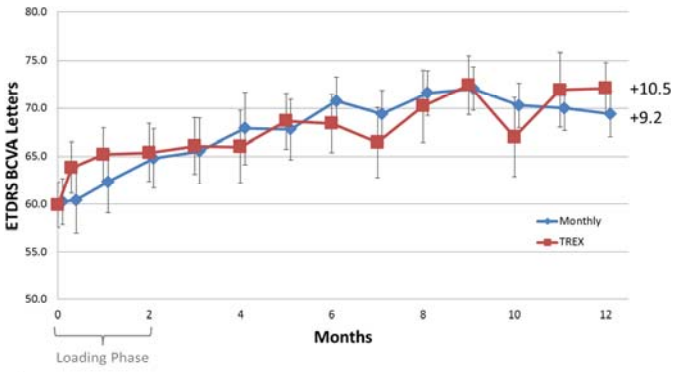
Kapusta amd part 2

McGill

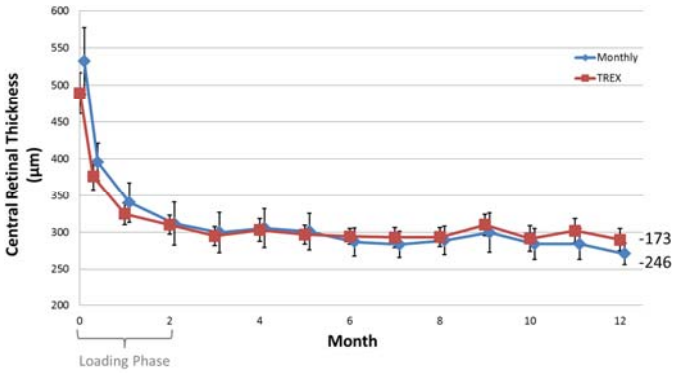


McGill



Cohort	Baseline ±SEM	Month 2 ±SEM	Month 6 ±SEM	Month 12 ±SEM
Monthly	60.3 ±2.4	64.8 ±3.1	70.8 ±2.5	69.4 ±2.4
TREX	59.9 ±2.4	65.4 ±3.0	68.7 ±3.0	72.1 ±2.7

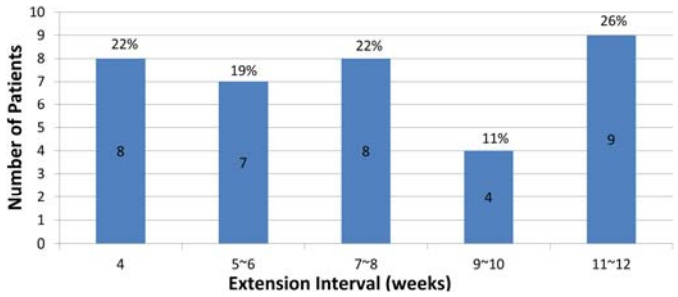
McGill



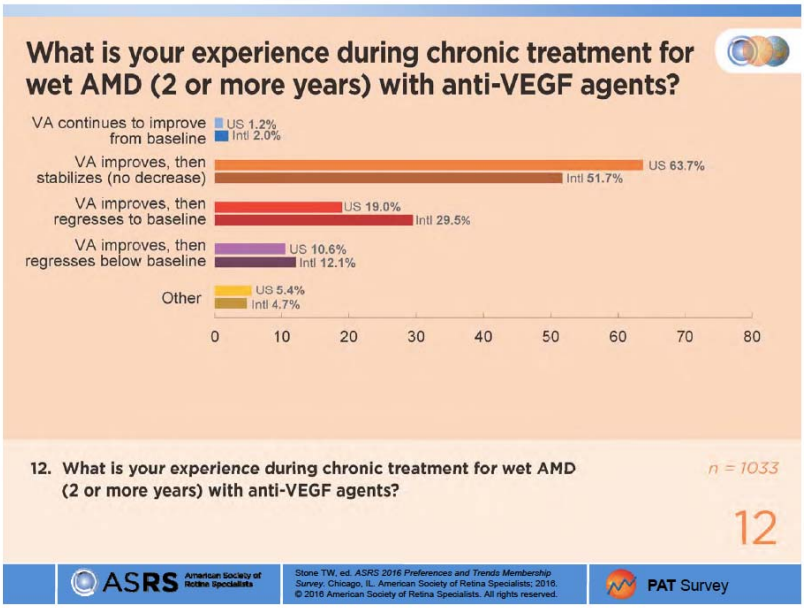
Cohort	Baseline ±SEM	Month 2 ±SEM	Month 6 ±SEM	Month 12 ±SEM
Monthly	533 ±45	312 ±29	287 ±19	271 ±15
TREX	489 ±28	310 ±13	294 ±11	290 ±15

TREX = Treat and Extend

McGill



McGill



McGill

Five-Year *Outcomes with Anti–Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration*

Maureen G. Maguire, PhD, Daniel F. Martin, MD, Gui-shuang Ying, PhD, Glenn J. Jaffe, MD, Ebenezer Daniel, MBBS, PhD, Juan E. Grunwald, MD, Cynthia A. Toth, MD, Frederick L. Ferris, MD, Stuart L. Fine, MD

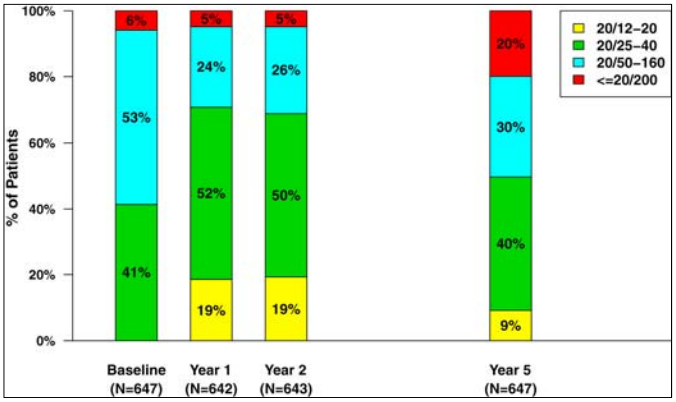
Ophthalmology Volume 123, Number 8, August 2016

Purpose: To describe outcomes 5 years after initiating treatment with bevacizumab or ranibizumab for neovascular age-related macular degeneration (AMD).
Design: Cohort study.
Participants: Patients enrolled in the Comparison of AMD Treatments Trials.
Methods: Patients were assigned randomly to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol. At 5 years, patients were recalled for examination.
Main Outcome Measures: Visual acuity (VA) and morphologic retinal features.
Results: Visual acuity was obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Most patients (60%) were treated 1 time or more with a drug other than their assigned drug. At the 5-year visit, 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse. Mean change in VA was −3 letters from baseline and −11 letters from 2 years. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm^2, a mean of 4.8 mm^2 larger than at 2 years. Geographic atrophy was present in 213 of 515 (41%) gradable eyes and was subfoveal in 85 eyes (17%). Among 555 eyes with spectral-domain optical coherence tomography, 83% had fluid (61% intraretinal, 38% subretinal, and 36% sub–retinal pigment epithelium). Mean foveal total thickness was 278 μm, a decrease of 182 μm from baseline and 20 μm from 2 years. The retina was abnormally thin (<120 μm) in 36% of eyes. Between 2 and 5 years, the group originally

Vision gains during the first 2 years were not maintained at 5 years

McGill

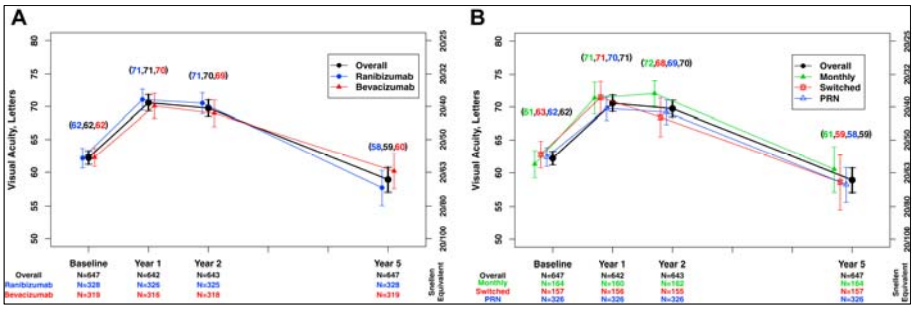
Distribution of visual acuity over time



Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology [Internet]. American Academy of Ophthalmology; 2016;123(8):1751–61.

McGill

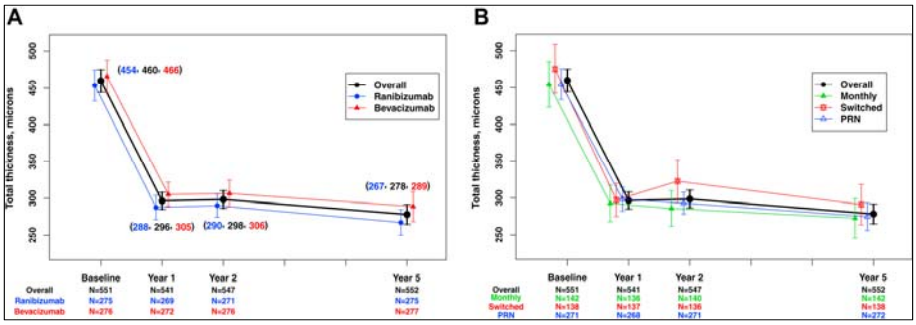
Mean visual acuity



Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology [Internet]. American Academy of Ophthalmology; 2016;123(8):1751–61.

McGill

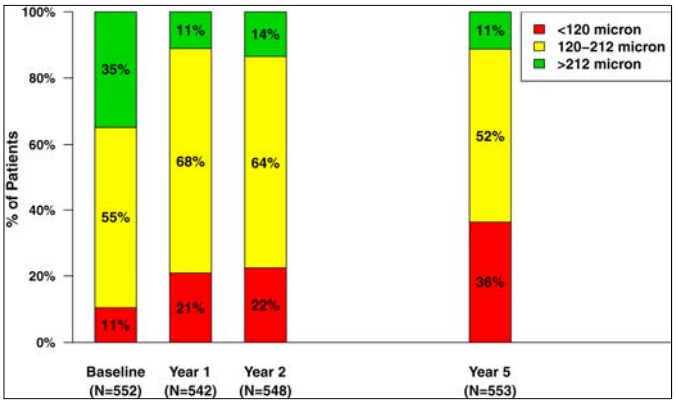
Mean total thickness at the foveal center



Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology [Internet]. American Academy of Ophthalmology; 2016;123(8):1751–61.

McGill

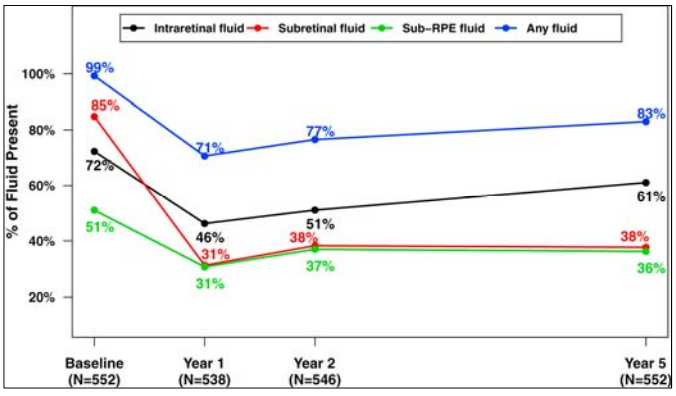
Retinal thickness at the foveal center



Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology [Internet]. American Academy of Ophthalmology; 2016;123(8):1751–61.

McGill

Percentage of eyes with fluid



Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying G, Jaffe GJ, Daniel E, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology [Internet]. American Academy of Ophthalmology; 2016;123(8):1751–61.

McGill

4. Other factors

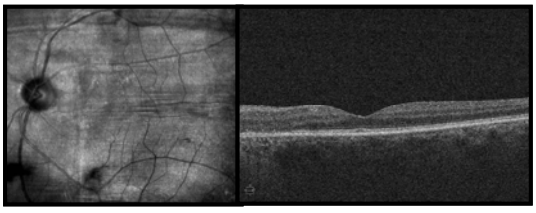
- Monocular status
- Status of the fellow eye and VA
- Patient preference – "Snowbirds"

McGill

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 6months F/U



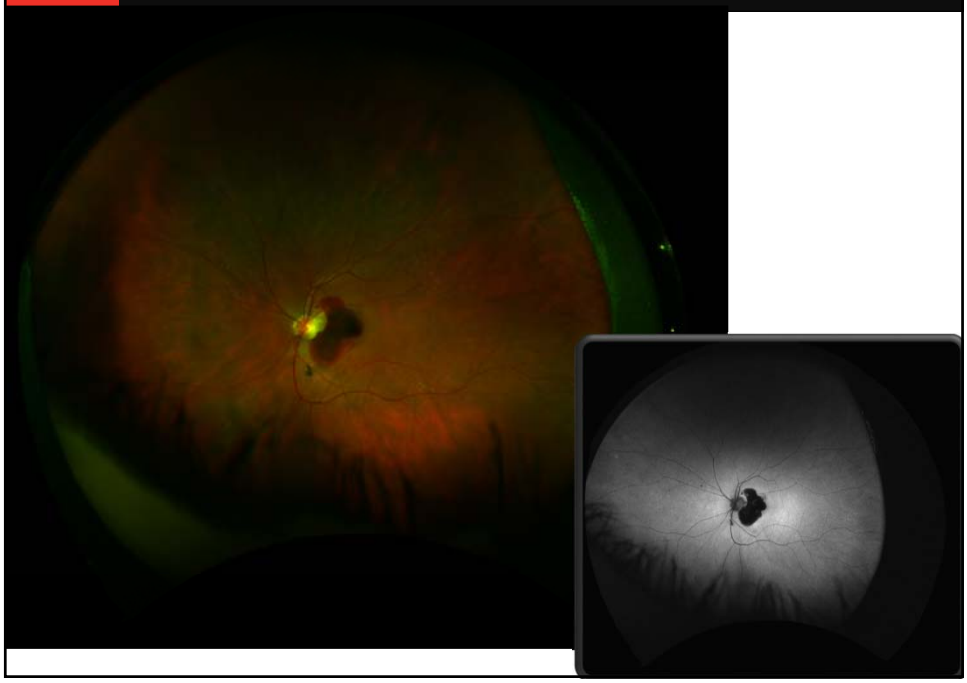
October 31st, 2016
VA 20/30
OCT dry
Last injection **18 months ago**

McGill

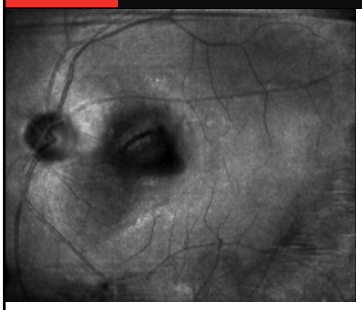
2 weeks after – Decreased VA

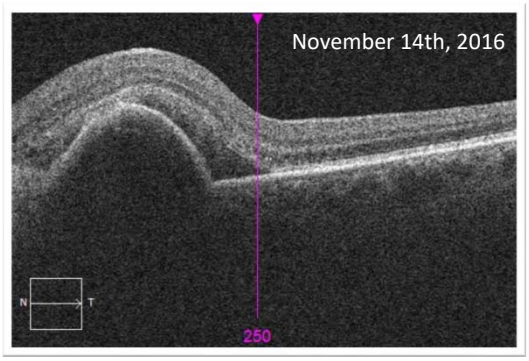
VA OS CF 1 feet

McGill

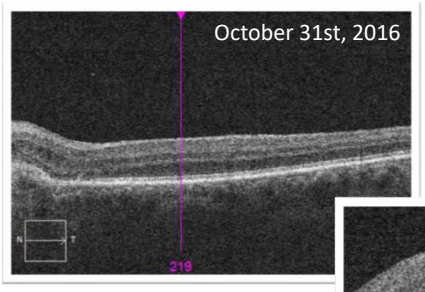


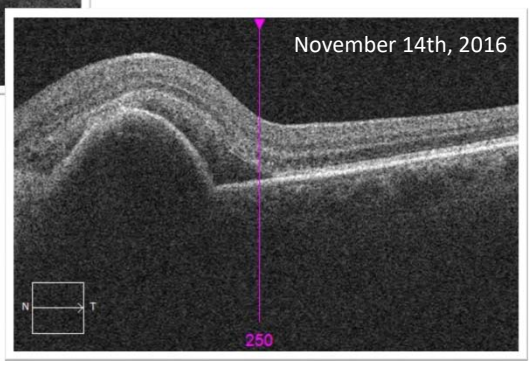
McGill



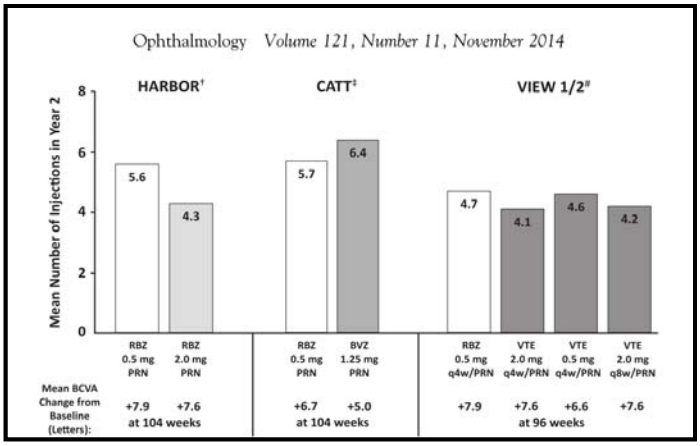


McGill





McGill



Ho AC, Busbee BG, Regillo CD, Wieland MR, Van Everen SA, Li 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

McGill

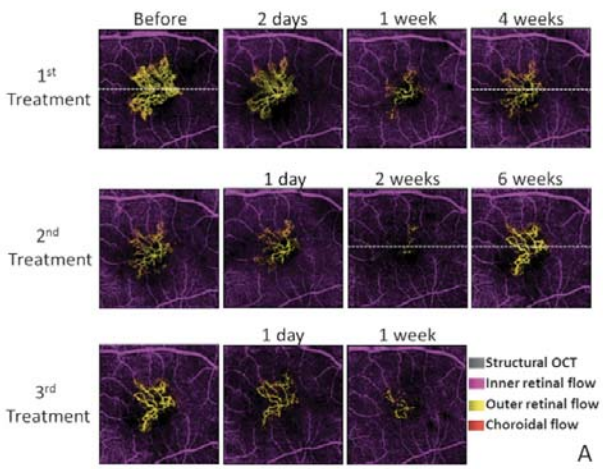
5. New Technologies

- **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,† OU TAN, PhD,*
BRUNO LUMBROSO, MD†

McGill



McGill

AMD Management : Teaching points

①Drug of choice

②Treatment Regimen

③ Signs for re-treatment

③ Signs for re-treatment

McGill

- 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.

McGill

PRN vs Monthly

A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study

GEETA A. LALWANI, PHILIP J. ROSENFELD, ANNE E. FUNG, SANDER R. DUBOVY, STEPHEN MICHELS, WILLIAM FEUER, JANET L. DAVIS, HARRY W. FLYNN, Jr, AND MARIA ESQUIABRO

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.

McGill

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 **≥100 µm**
  - Loss of **≥5 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.

McGill

- 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.

McGill

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.**

McGill

Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration

Allen C. Ho, MD,[1] Brandon G. Busbee, MD,[2] Carl D. Regillo, MD,[1] Mark R. Wieland, MD,[3] Sheri A. Van Everen, PharmD,[3] Zhengrong Li, PhD,[3] Roman G. Rubio, MD,[3] Phillip Lai, MD,[3] for the HARBOR Study Group*

Objective: To evaluate the 24-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly or as needed (pro re nata [PRN]) in patients with neovascular age-related macular degeneration (wet AMD).

Design: Twenty-four-month, multicenter, randomized, double-masked, active treatment-controlled phase 3 trial.

Participants: Patients (n = 1098) ≥50 years of age with treatment-naïve subfoveal wet AMD.

Methods: Patients were randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg monthly or PRN after 3 monthly loading doses.

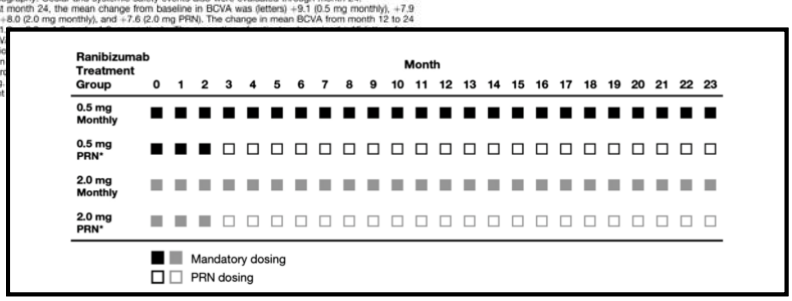
Main Outcome Measures: The primary efficacy end point was the mean change in best-corrected visual acuity (BCVA) from baseline at month 12. Key secondary end points included mean change in BCVA from baseline at month 24, proportion of patients who gained ≥15 letters in BCVA, mean number of ranibizumab injections, and mean change in central foveal thickness from baseline over time by spectral-domain optical coherence tomography. Ocular and systemic safety events also were evaluated through month 24.

Results: At month 24, the mean change from baseline in BCVA was (letters) +9.1 (0.5 mg monthly), +7.9 (0.5 mg PRN), +8.0 (2.0 mg monthly), and +7.6 (2.0 mg PRN). The change in mean BCVA from month 12 to 24 was (letters) −1.
baseline in BCV
bizumab injectio
were required in
0.5 mg PRN gro
monthly dosing.
were consistent

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 Medi- tec, Inc., Dublin, CA).*



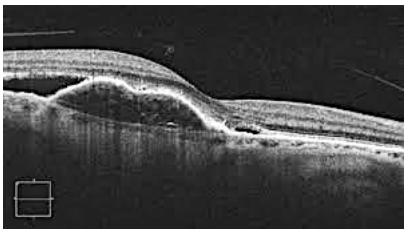
McGill

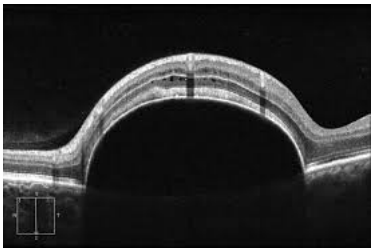
- Monitor disease activity using SD-OCT, and on a monthly base.
- Concept of a **'zero tolerance'**
- However, persistent intraretinal cysts should be considered signs of irreversible retinal degeneration and should not trigger further retreatment.

These recommendations are based on evidence levels I (CATT, VIEW, HARBOR) and evidence levels

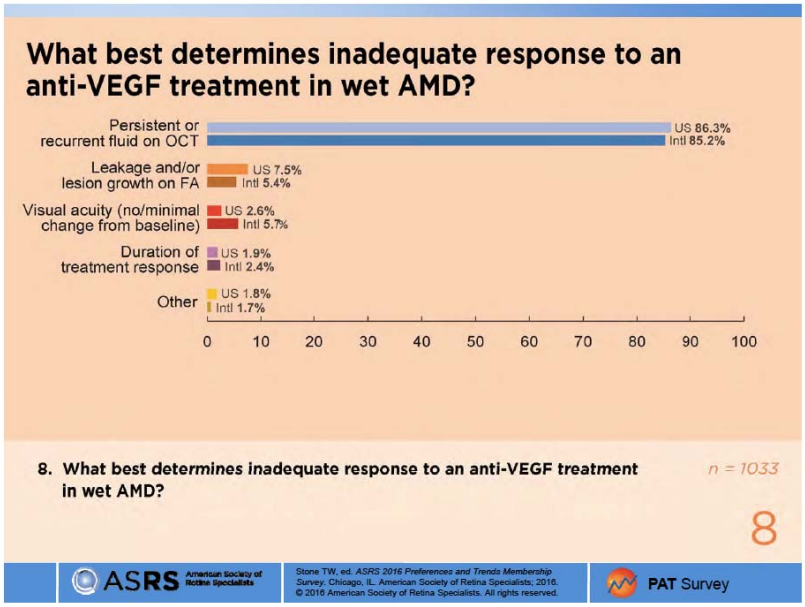
McGill

- **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.



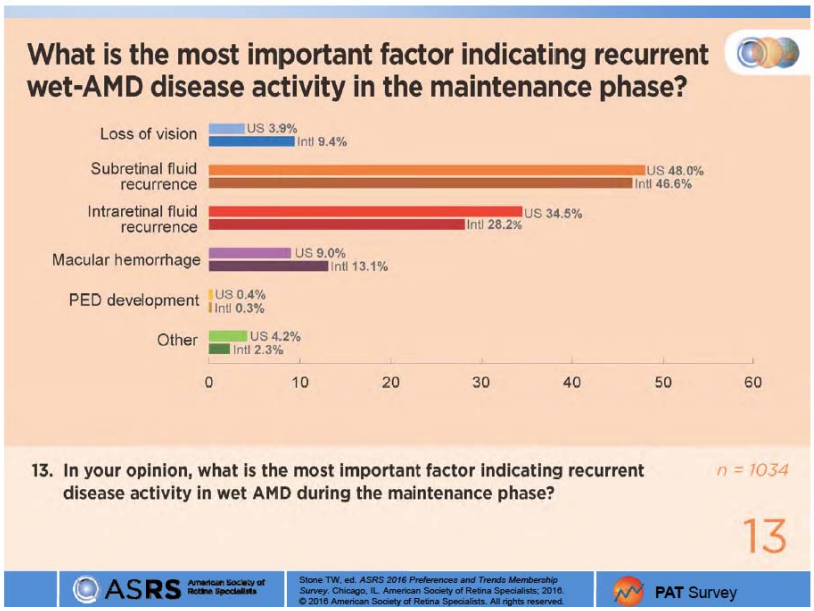


McGill

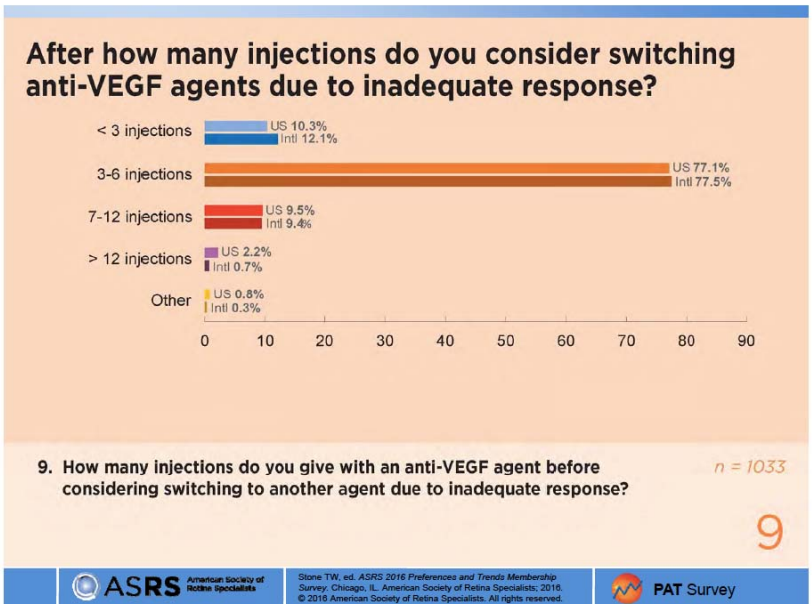


McGill

Teaching points



McGill



McGill

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 Aflibercept

Sophie Seguin-Greenstein,[1,2] Sue Lightman,[1,2,3] and Oren Tomkins-Netzer[1,2,3,4]

[1] *Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK*
[2] *UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK*
[3] *Royal Surrey County Hospital, Egerton Road, Guildford, Surrey GU2 7XX, UK*
[4] *Bnai Zion Medical Center, 47 Golomb Road, 31048 Haifa, Israel*

Correspondence should be addressed to Oren Tomkins-Netzer; o.tomkins-netzer@ucl.ac.uk

Received 31 August 2015; Accepted 11 January 2016

Academic Editor: Naoshi Kondo

With the introduction of aflibercept, eyes with neovascular age-related macular degeneration (AMD) not responding well to injections of ranibizumab or bevacizumab can be switched to treatment with aflibercept. We carried out a meta-analysis to analyze all available evidence of visual and anatomical outcomes of eyes with resistant neovascular AMD switched to aflibercept at six months. Data from seven retrospective and prospective studies looking at change in best corrected visual acuity (BCVA) and central retinal thickness (CRT) were included. Weighted mean difference (WMD) and 95% CI were estimated using the standardized mean change method. The overall results of the meta-analysis showed a small but statistically significant improvement in BCVA six months following treatment switch to aflibercept (WMD 0.142, 95% CI 0.006 to 0.28; $p = 0.04$), and the effect was more significant in data gathered from prospective studies (WMD 0.407, 95% CI 0.023 to 0.791, $p = 0.038$). There was a significant improvement in CRT following treatment switch to aflibercept (WMD −0.36, 95% CI −0.485 to −0.235; $p < 0.0001$). Our meta-analysis indicates that following treatment switch to aflibercept patients may have a significant improvement in CRT with stabilization or even some improvement in their visual acuity.

Journal of Ophthalmology Volume 2016, Article ID 4095852

McGill

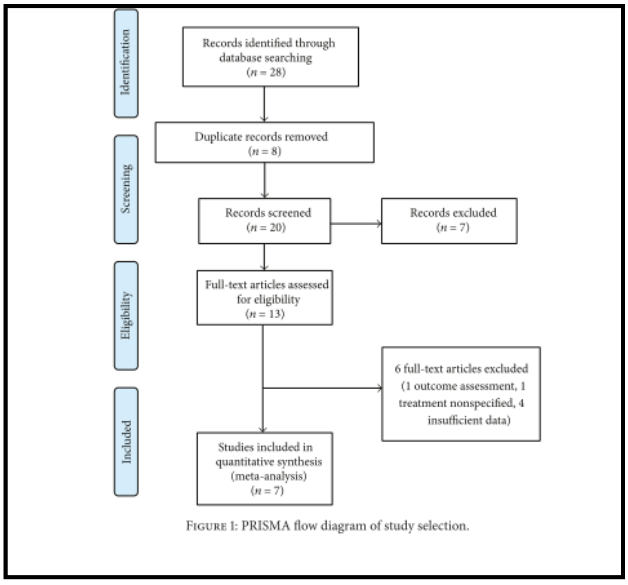


FIGURE 1: PRISMA flow diagram of study selection.

McGill

Only 3 PROSPECTIVE STUDIES

Table 1: Characteristics of all studies included in the Meta Analysis.

Authors	Year	Country	Study design	N (eyes)	Inclusion/exclusion criteria	Matching/comparable factors	Study quality (points scoring scale)
Kumar [24]	2013	USA	Retro	34	IRF, SRF or sub-RPE with adjacent IRF/SRF on OCT	*BCVA, CRT*	Selection: 2 Comparability: 2 Stats:1 Outcome: 6 Overall: 11
Bakall [25]	2013	USA	Retro	36	CNV confirmed by OCT and FFAat baseline visit IRF/SRF present at least for 3 months prior to conversion and treated with 3 monthly anti VEGF injections	*BCVA, CRT*	Selection: 3 Comparability: 3 Stats: 1 Outcome: 4 Overall: 11
Gharbiya [26]	2014	Italy	Retro	31	IRF/SRF on OCT At least 6 previous antiVEGF injections Less than 4 weeks between last anti-VEGF treatment and conversion	*BCVA, CRT*	Selection: 2 Comparability: 2 Stats: 3 Outcome: 6 Overall: 13
Messenger [27]	2014	USA	Retro	109	IRF, SRF or sub-RPE with adjacent IRF/SRF on OCT At least 12 months of anti VEGF treatment prior to conversion VA > 20/400 at conversion At least 12 months follow up	*CRT*	Selection: 2 Comparility: 3 Stats: 2 Outcome: 4 Overall: 11
Wykoff [28]	2014	USA	Prosp	46	Patients who completed the 2 years SAVE trial	*BCVA,CRT*	Selection: 3 Comparability: 3 Stats: 3 Outcome: 6 Overall: 15
Chang [29]	2014	Australia	Prosp	50	CNV on OCT and FFA At least 4 anti VEGF injections prior to conversion	*BCVA*	Selection: 3 Comparability: 2 Stats: 3 Outcome: 6 Overall: 14
Singh [30]	2014	USA	Prosp	26	Active CNV confirmed by FFA BCVA between 25–80 ETDRS letters at baseline At least one antiVEGF injection within 3 months of conversion	*BCVA*	Selection: 3 Comparility: 2 Stats: 3 Outcome: 6 Overall: 14

McGill

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

Authors	Mean age (years)	Duration of disease (months)	Nb of injections prior to conversion	Time between last antiVEGF and conversion	Mean time of follow up (months)	Mean number aflibercept injections	Treatment regimen
Kumar [24]	79 (IQR 72–84)	44.7 (IQR 24–76)	28.6 (IQR 10–47)	34.4 days (IQR 32–37)	6	5.6 (NS)	Loading then PRN
Bakall [25]	79 (range 60–88)	NS	25.6 (6–74)	NS	6	5.2 (4–6)	Loading then PRN
Gharbiya [26]	70.1 (range 60–86)	41.3 (15–58)	34.4 (15–50)	5.1 weeks (range 4–6)	6	4.5 (3–6)	Loading then PRN
Messenger [27]	80.3 (range 59–96)	NS	21.4 (4–60)	NS	6, 12	7.2 (1–12) for 12 months. NS at 6 months	Loading then PRN
Wykoff [28]	77.8 (range 55–95)	NS	42 (19–67)	33 days (range 28–68)	6	5.6 (4–6)	Loading then PRN
Chang [29]	77.8 (NS)	40	34.94	NS	6	NS	Loading then bimonthly
Singh [30]	78 (NS)	14	9.62 (3–23)	50 days (range 21–91)	6	NS	Loading then bimonthly

McGill

- 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.

McGill

TAKE HOME MESSAGES

① Drug of choice

Hospital-Private setting-Country

$$

Clinical Scenario (PCV, RAP..)

② Treatment Regimen

T&E / PRN

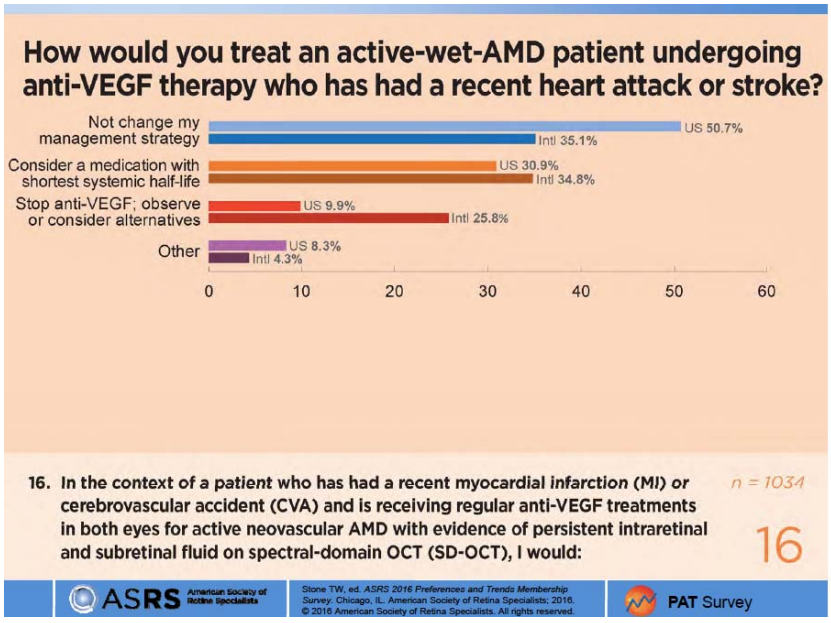
If PRN – monthly follow-up

③ Follow-up / Re-treatment signs

SD-OCT / SS-OCT

OCT-A

McGill


How would you treat an active-wet-AMD patient undergoing anti-VEGF therapy who has had a recent heart attack or stroke?
Not change my management strategy
US 50.7%
Intl 35.1%
Consider a medication with shortest systemic half-life
US 30.9%
Intl 34.8%
Stop anti-VEGF; observe or consider alternatives
US 9.9%
Intl 25.8%
Other
US 8.3%
Intl 4.3%
0
10
20
30
40
50
60
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:
n = 1034
16
ASRS American Society of Retina Specialists
Stone TW, ed. ASRS 2016 Preferences and Trends Membership Survey. Chicago, IL: American Society of Retina Specialists; 2016.
© 2016 American Society of Retina Specialists. All rights reserved.
PAT Survey

McGill

② Treatment Regimen