Kapusta AMD Part 1

Management of Neovascular AMD

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FINANCIAL DISCLOSURES

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

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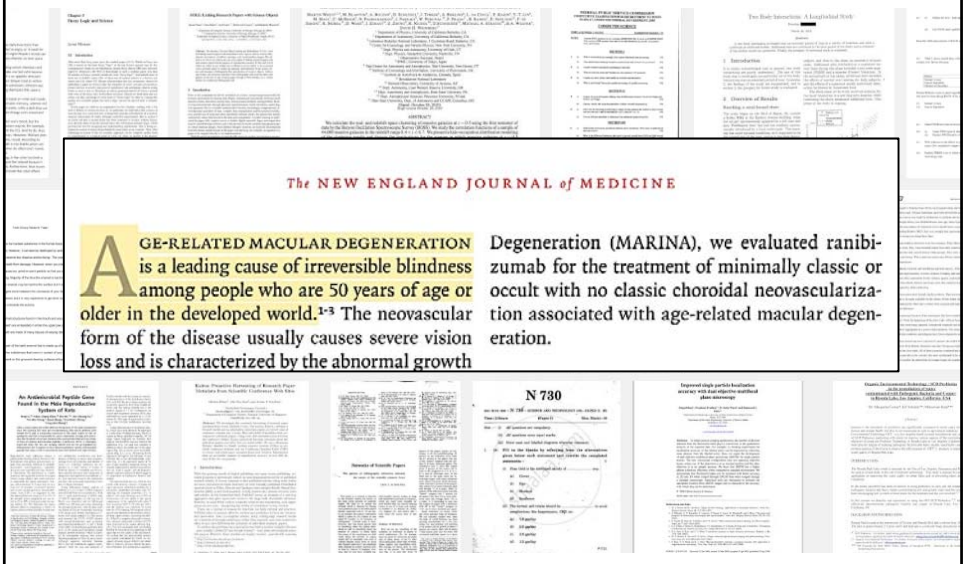
Background

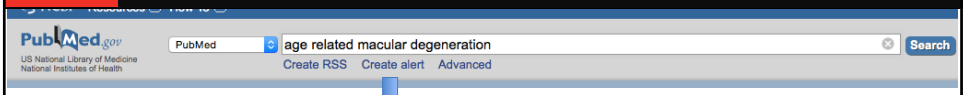


The NEW ENGLAND JOURNAL of MEDICINE

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.[1-3] The neovascular form of the disease usually causes severe vision loss and is characterized by the abnormal growth

Degeneration (MARINA), we evaluated ranibizumab for the treatment of minimally classic or occult with no classic choroidal neovascularization associated with age-related macular degeneration.

Background



Search Results: 25174

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Search Results: 15528 → **62.7%**

"Anti-VEGF Era"

AMD Management : Teaching points

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

①Drug of choice

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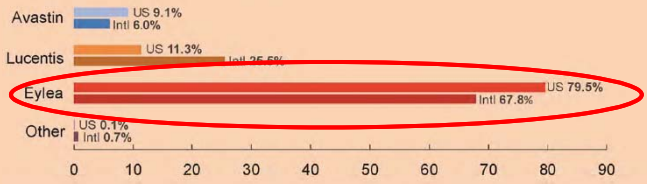
① Drug of choice

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 (aflibercept, 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)?

n = 1034

5

ASRS American Society of Retina Specialists

PAT Survey

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Visual outcomes in major treatment trials of **neovascular AMD**

		Treatment	Control	Duration of follow-up (years)	Mean change in visual acuity in treatment group (letters)	Mean change in visual acuity in control group (letters)
Laser	MPS (extrafoveal)[64]	Laser	Placebo	5	−25	−35
	MPS (juxtafoveal)[65]	Laser	Placebo	5	−25	−30
	MPS (subfoveal)[66]	Laser	Placebo	4	−20	−25
PDT	TAP[26]	Photodynamic therapy	Placebo	2	−13	−19
	VIM[67]	Photodynamic therapy	Placebo	2	−2	−21
	VIP[68]	Photodynamic therapy	Placebo	2	−19	−25
Anti-VEGF	ANCHOR[2]	Ranibizumab 0·5 mg monthly	Photodynamic therapy	2	+7	−15
	MARINA[1]	Ranibizumab 0·5 mg monthly	Placebo	2	+11	−10
	PRONTO[69]	Ranibizumab 0·5 mg monthly for 3 months then as needed	NA	2	+10·7	NA
	SUSTAIN[24]	Ranibizumab 0·5 mg monthly for 3 months then as needed	NA	1	+6·7	NA
	SAILOR[70]	Ranibizumab 0·5 mg monthly for 3 months then as needed	NA	1	+2·3	NA
	CATT[3]	Bevacizumab 1·25 mg monthly	Ranibizumab 0·5 mg monthly	1	+8	+8·5
	VIEW 1	Aflibercept 2 mg two-monthly	Ranibizumab 0·5 mg monthly	1	+7·9	+8·1
	VIEW 2	Aflibercept 2 mg two-monthly	Ranibizumab 0·5 mg monthly	1	+8·9	+9·4

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

De Jong PT. Age-related macular degeneration. N Engl J Med. Elsevier Ltd; 2006;355(9827):1728–38.

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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 oligonucleic acid 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.

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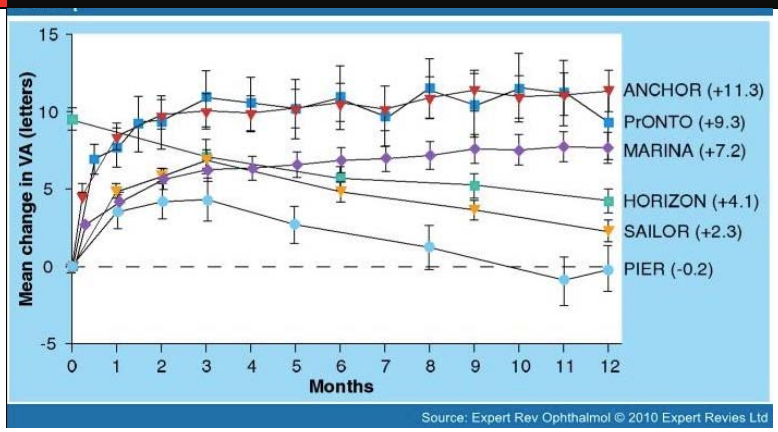

Visual acuity changes with ranibizumab. Mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) letters through:

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 Intra-Ocular 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

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N Engl J Med. 2011 May 19; 364(20): 1897–1908. doi:10.1056/NEJMoa1102673.

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 a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD 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 non-inferiority limit of 5 letters on the eye chart.

RESULTS—Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, $P = 0.03$ by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS—At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.)

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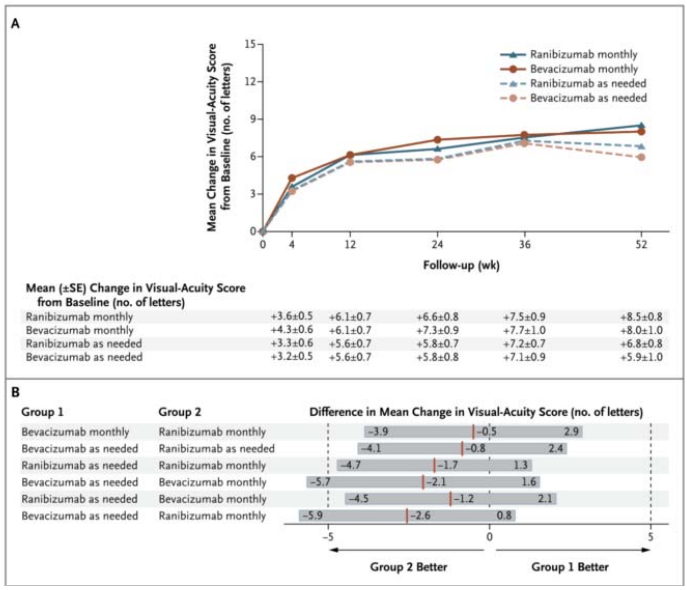
Change in Visual-Acuity Score from Baseline to 1 Year



Mean (±SE) Change in Visual-Acuity Score from Baseline (no. of letters)

Ranibizumab monthly	+3.6±0.5	+6.1±0.7	+6.6±0.8	+7.5±0.9	+8.5±0.8
Bevacizumab monthly	+4.3±0.6	+6.1±0.7	+7.3±0.9	+7.7±1.0	+8.0±1.0
Ranibizumab as needed	+3.3±0.6	+5.6±0.7	+5.8±0.7	+7.2±0.7	+6.8±0.8
Bevacizumab as needed	+3.2±0.5	+5.6±0.7	+5.8±0.8	+7.1±0.9	+5.9±1.0

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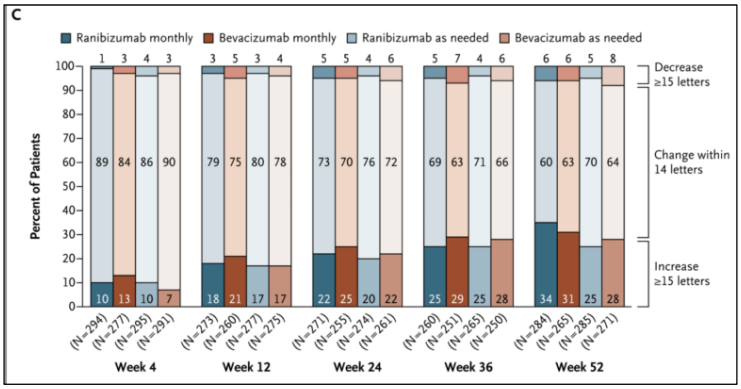
Change in Visual-Acuity Score from Baseline to 1 Year



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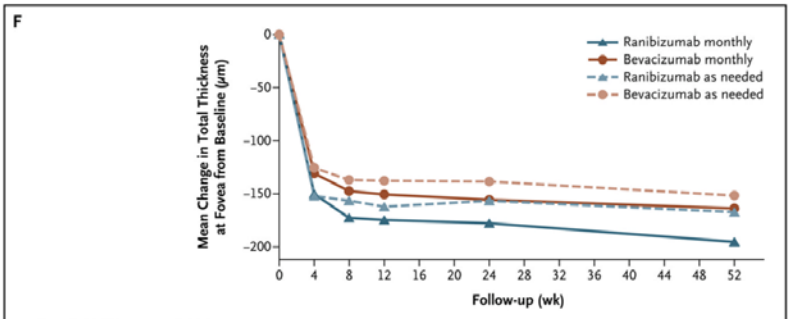
Findings on Optical Coherence Tomography



Mean (±SE) Change in Thickness at Fovea from Baseline (μm)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Ranibizumab monthly	−151±9	−173±9	−175±10	−178±10	−196±11
Bevacizumab monthly	−131±9	−147±9	−151±10	−156±11	−164±11
Ranibizumab as needed	−153±9	−157±10	−163±11	−157±11	−168±11
Bevacizumab as needed	−126±8	−137±9	−138±10	−139±10	−152±11

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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 (PlGF)** present on endothelial cells and leucocytes.

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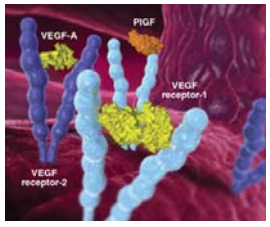
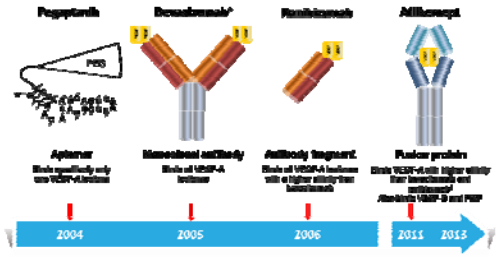
Anti- VEGF therapy



- **Aflibercept (VEGF Trap-Eye,Regeneron/Bayer)**

	Structure	Molecular weight	Mechanism of action	Binding affinity to VEGF-A_{165}
Aflibercept	Fusion protein: domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused with IgG1 Fc[15]	115 kDa[37]	Binds to all isoforms of VEGF-A, VEGF-B, and PlGF[15]	0.5 pM[15]
Ranibizumab	Monoclonal IgG antibody fragment (Fab)[12]	48 kDa[44]	Binds to all isoforms of VEGF-A[44]	46 pM[37]
Bevacizumab	Monoclonal IgG antibody[40]	149 kDa[37]	Binds to all isoforms of VEGF-A[41]	58 pM[37]

Abbreviations: VEGF, vascular endothelial growth factor; IgG, immunoglobulin G.



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Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

Jeffrey S. Heier, MD,[1] David M. Brown, MD,[2] Victor Chong, MD,[3] Jean-Francois Korobelnik, MD,[4] Peter K. Kaiser, MD,[5] Quan Dong Nguyen, MD,[6] Bernd Kirchhof, MD,[7] Allen Ho, MD,[8] Yuichiro Ogura, MD,[9] George D. Yancopoulos, MD, PhD,[10] Neil Stahl, MD,[10] Robert Vitti, MD,[10] Alyson J. Berliner, MD, PhD,[10] Yuhwen Soo, PhD,[10] Majid Anderesi, MD,[11] Georg Groetzbach, MD,[11] Bernd Sommerauer, PhD,[11] Rupert Sandbrink, MD, PhD,[11,12] Christian Simader, MD,[13] Ursula Schmidt-Erfurth, MD,[13] for the VIEW 1 and VIEW 2 Study Groups*

Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer

- **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.**

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2012;119:2537–2548 © 2012 by the American Academy of Ophthalmology.

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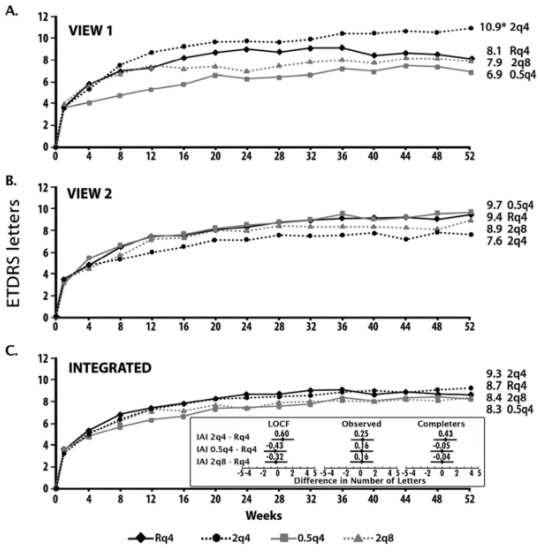
Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis.



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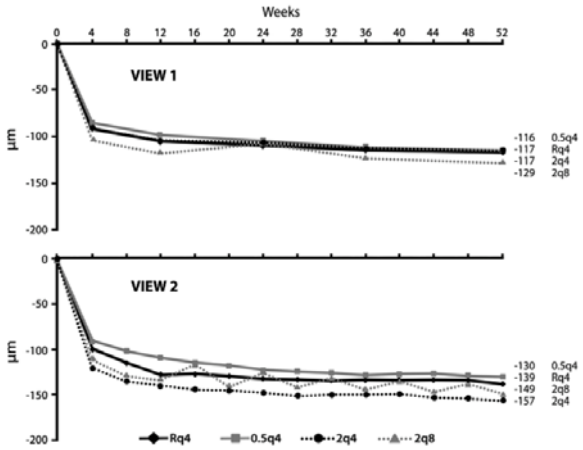
Mean change from baseline in central retinal thickness



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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".**

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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).

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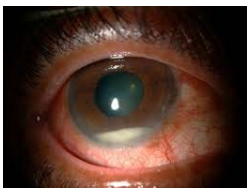
How are they different?



#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.

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How are they different?

#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.

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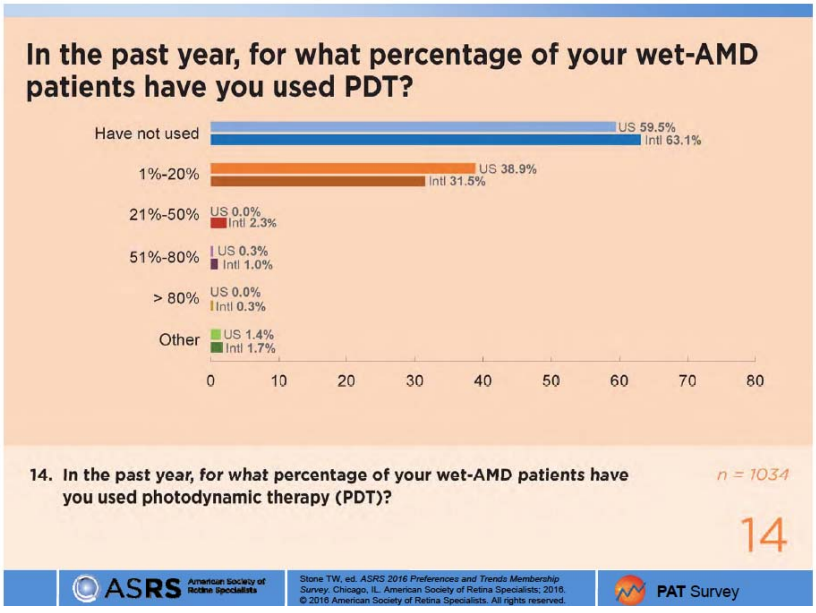

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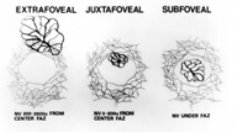
- **Laser photocoagulation** therapy and **verteporfin PDT** have shown benefits compared with the natural course in selected subtypes and stages of neovascular AMD.
- Application of photocoagulation or PDT for subretinal new vessels is likely to be considered in current clinical practice in less common 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.



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Polypoidal Choroidal Vasculopathy

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

The EVEREST study is the first multi-center, double-masked, indocyanine green angiography (ICG-A)-guided randomized controlled trial with an angiographic treatment outcome designed to assess the effect of Visudyne® (verteporfin photodynamic therapy) alone or in combination with Lucentis® (ranibizumab) compared with Lucentis® alone in patients with symptomatic macular polypoidal choroidal vasculopathy (PCV)

- **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:
  - 77.8% of patients who received the Visudyne® – Lucentis®
  - 71.4% of Visudyne® monotherapy
  - 28.6% 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)

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Intravitreal Aflibercept and Ranibizumab Injections for Polypoidal Choroidal Vasculopathy

HAN JOO CHO, KYOUNG MIN KIM, HYOUNG SEOK KIM, JUNG IL HAN, CHUL GU KIM, TAE GON LEE, AND JONG WOO KIM

• PURPOSE: To compare the effectiveness of intravitreal injection of aflibercept and ranibizumab for patients with polypoidal choroidal vasculopathy (PCV).

POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV) IS a clinical condition that is generally classified as a subtype of neovascular age-related macular degener-

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.

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AMD Management : Teaching points

①Drug of choice

②Treatment Regimen

③ Signs for re-treatment

② Treatment Regimen

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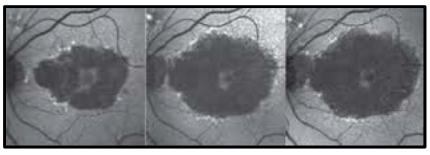
1. Continuous Treatment

- 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.*



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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.

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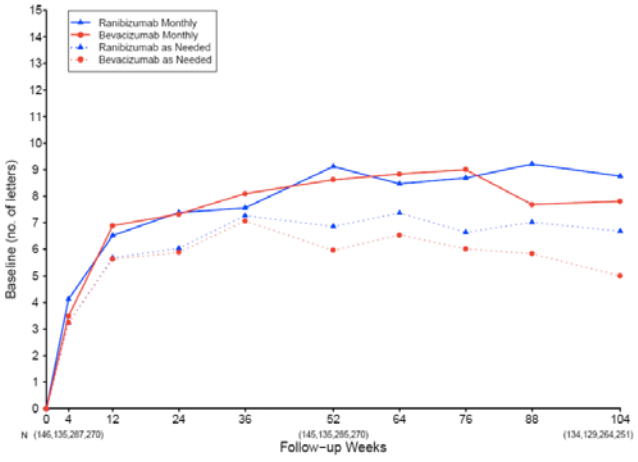

Figure 2.
Patients treated with the same dosing regimen for 2 years: mean change in visual acuity from enrollment, over time.

Ophthalmology ,2012 July ; 119(7): 1388–1398

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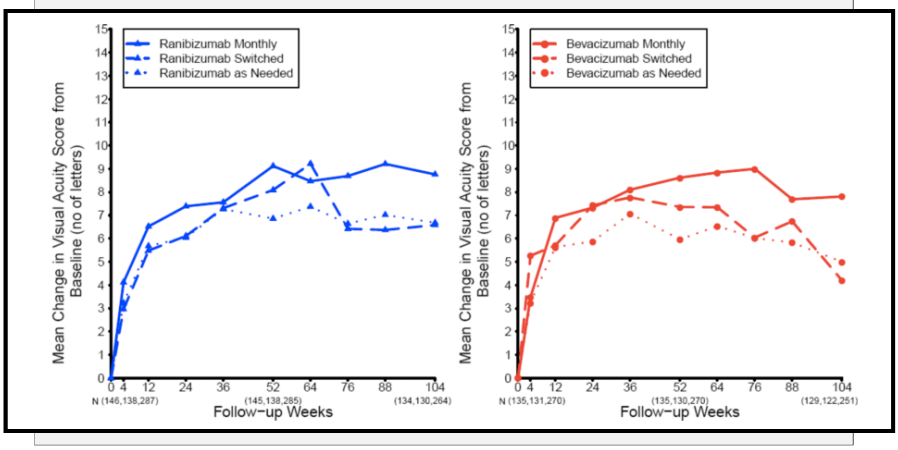
- Eyes that switched from monthly to as-needed treatment experienced a greater mean decrease in vision during year two and a lower proportion of eyes had no fluid.



Ophthalmology ,2012 July ; 119(7): 1388–1398

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3. Treat and Extend

- Customized or Individualized
- Lower risk of geographic atrophy compared with that observed with continuous monthly treatment

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Br J Ophthalmol. 2015 Oct 29. pii: bjophthalmol-2015-306987. doi: 10.1136/bjophthalmol-2015-306987. [Epub ahead of print]

A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration.

Chin-Yee D[1], Eck T[1], Fowler S[2], Hardi A[2], Apte RS[1].

Author information

Abstract

PURPOSE: To evaluate the relative efficacy of as needed versus treat and extend regimen for the treatment of neovascular age-related macular degeneration (AMD).

METHODS: We conducted a systematic review of studies that evaluated the efficacy of as needed or treat and extend regimen for neovascular AMD by searching multiple databases up to December 2013. Included studies were selected based on study duration of no less than 12 months, availability of outcome data, treatment protocol for as needed groups or pro re nata (PRN) receiving bevacizumab

these regimens compared with monthly therapy.

KEYWORDS: Angiogenesis; Degeneration; Drugs; Macula; Treatment Medical

Systematic Review:The study suggests superiority of Treat and Extend regimen to PRN in a 12 month period

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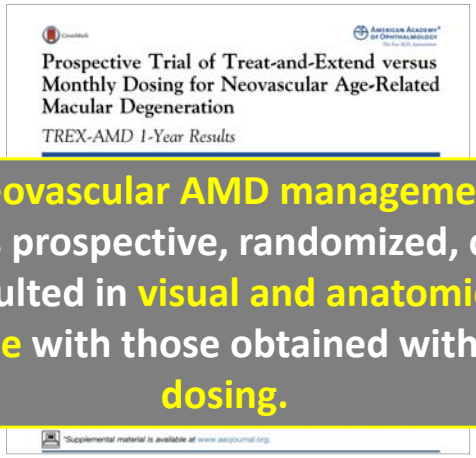
*Prospective Trial of **Treat-and-Extend** versus **Monthly Dosing** for Neovascular Age-Related Macular Degeneration*

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, SriniVas R. Sadda, MD



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

TREX-AMD 1-Year Results

"Supplemental material is available at www.aaojournal.org.

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.

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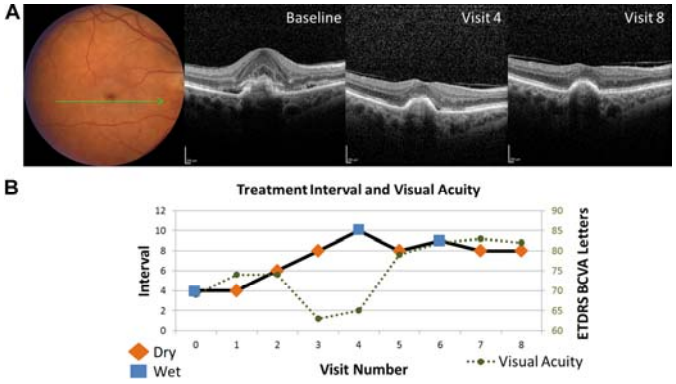

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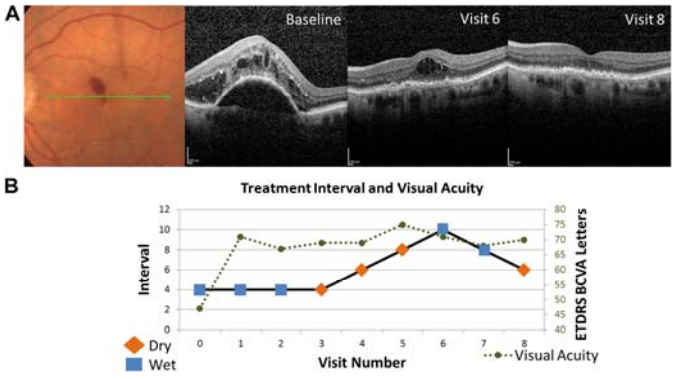
A
Baseline
Visit 6
Visit 8
B
Treatment Interval and Visual Acuity
Interval
ETDRS BCVA Letters
Visit Number
Dry
Wet
Visual Acuity