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Will Individualized Therapy Become Standard of Care for Age-related Macular Degeneration?

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Treatment of the wet variety of age-related macular degeneration (AMD), the most common cause of blindness in the elderly, has undergone a significant change in the past 30 years with the introduction of anti-vascular endothelial growth factor (VEGF) agents. This issue of *Ophthalmology Scientific Update* outlines the similarities and differences of the agents in this class and the clinical trial data supporting their effectiveness and safety in patients with wet AMD, as well as comparisons of monthly injections with a treat-and-extend strategy.

Age-related macular degeneration (AMD) is the principal cause of blindness among elderly patients in developed nations.[1] The condition can be classified into dry (non-exudative or non-neovascular) and wet (exudative or neovascular) types.[2] While dry AMD is more prevalent, accounting for almost 90% of AMD cases, wet AMD is more severe and often implicated in vision loss. Wet AMD is characterized by angiogenesis, the abnormal growth of new fragile blood vessels under the macula. This can lead to the leakage of fluid, bleeding, or the development of retinal edema.[3,4] If left untreated, neovascularization can damage the photoreceptors and the retinal pigment epithelial cells, causing irreversible vision loss.

Over the past 30 years, the treatment of wet AMD has undergone significant advances: from thermal laser in the 1980s to photodynamic therapy (PDT) in the early 2000s,[5] and finally moving into the use of anti-vascular endothelial growth factor (VEGF) agents. The development of anti-VEGF therapies is based on the findings that VEGF plays a key role in the pathogenesis of choroidal neovascularization (CNV).[6,7] Currently, 2 anti-VEGF agents are routinely administered in Canadian ophthalmology practices: Health Canada-approved ranibizumab (Lucentis®) and the off-label use of bevacizumab (Avastin®). A third – aflibercept (Eylea®) – is approved by the United States Food and Drug Administration, and a decision by Health Canada is pending. Although effective, frequent intravitreal anti-VEGF injections pose a significant inconvenience to patients and their caregivers, especially if they have to travel great distances to receive treatment. Significant costs associated with ranibizumab also present a significant burden to provincial health care budgets. Finally, the expected shortage of ophthalmologists in Canada[8] is expected to exacerbate the existing challenge of timely patient care, as the administration of anti-VEGF injections requires specialized training. Thus, there has been a growing interest in finding the anti-VEGF treatment regimen that would maximize the benefits of the therapy while reducing the burden of its administration.

AMD in Canada: Prevalence, Trends, and Disease Burden

According to the latest estimates, nearly 1 million Canadians currently have some degree of AMD-associated visual impairment.[9] Of these, 250 000 have an advanced form of the disease and 64 000 are legally blind. Furthermore, with an aging population these numbers are expected to double in the next 25 years.[9] The progressive downward trend in the ophthalmologist-to-population ratio raises the question as to whether the number of trained ophthalmology specialists will be able to fulfill the demands.[8]

AMD is a condition associated with a high socioeconomic burden. Direct costs associated with the disease include the costs of screening, treatment, and vision support services. Individuals affected with AMD are at greater risk of depression and injury due to falls, leading to increased medical costs. Thus, beyond the economic cost and significant contribution to the $7.9 billion

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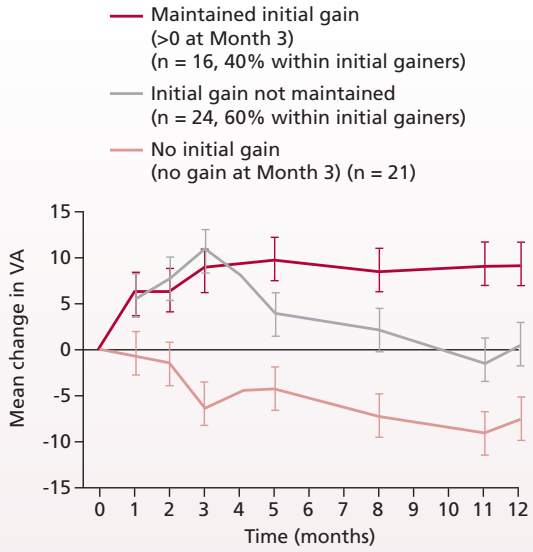
Figure 1: PIER VA subset analysis: Mean change in VA from baseline for 3 subgroups of patients



VA = visual acuity
Data on file, Novartis

estimated annual costs of vision loss in Canada,[9] AMD also has serious emotional consequences for patients, their families and caregivers.[10,11] It has been suggested that the costs of medical resources, including the nonmedical devices and the cost of transportation, rise significantly with decreased visual acuity (VA).[11]

Currently, ranibizumab is reimbursed in the majority of Canadian provinces, with some differences in reimbursement programs between British Columbia[12] and Nova Scotia[13] and the rest of the country. Some insurance plans, however, require that the patient pay a percentage of the medication cost and/or administration-related fees.[14] In some instances, this co-payment might be significant and deter a clinician from initiating a drug that is on the provincial formulary.

Taking into consideration the significant economic, social and personal toll of the disease and the complexity in the reimbursement plan, one can comprehend the ongoing need to assure adequate access to the best available therapies for all AMD patients in Canada.[15]

Intravitreal Anti-VEGF Therapies: Mechanism of Action and Pharmacological Properties

As mentioned, there are 2 intravitreal anti-VEGF therapies widely used in Canada: ranibizumab (approved) and bevacizumab (off-label). Although these 2 agents and aflibercept have a similar mode of action, their pharmacological properties differ.[16-18] While ranibizumab is a humanized, monoclonal antibody fragment, bevacizumab and aflibercept are full-length antibodies.

The localized versus systemic antibody effects of bevacizumab and ranibizumab have been studied in several animal models.[19-22] The vitreous half-life of ranibizumab is shorter than

Table 1: PrONTO re-treatment criteria[42]

- 5-letter visual loss associated with macular fluid noted on OCT
- A 100 µm increase in CRT by OCT
- New-onset classic CNV
- New macular hemorrhage
- Persistent macular fluid detected by OCT after the last injection

OCT = ocular coherence tomography; CRT = central retinal thickening; CNV = choroidal neovascularisation

for bevacizumab, with higher peak concentrations of drug identified in the aqueous humor of the bevacizumab-treated eye. In trials comparing the pharmacokinetics of intravitreally administered ranibizumab and bevacizumab in rabbits, ranibizumab was below the limit of detection in the uninjected fellow eye as well as in the systemic circulation; however, small quantities of bevacizumab were identified in both the systemic circulation and the uninjected eye.[19,20] Results of the recently conducted IVAN trial, which compared ranibizumab with bevacizumab for the treatment of neovascular AMD, demonstrated significant reduction in serum VEGF levels with bevacizumab compared to ranibizumab.[23] It is believed that the Fc fragment of bevacizumab facilitates transport of the molecule from the eye into the systemic circulation.[24]

Aflibercept has been shown to bind human VEGF with higher affinity and a significantly faster association rate than ranibizumab and bevacizumab.[18,25] Endothelial cell proliferation assays, conducted by Yu et al,[17] confirmed that bevacizumab was 11-fold and 35-fold less potent than ranibizumab and aflibercept, respectively.

The suggestion that aflibercept has a 140-fold higher binding affinity for VEGF than ranibizumab led to an assumption that the biological activity of aflibercept at 10–12 weeks after an intravitreal injection may be comparable to that of an equimolar amount of ranibizumab at 30 days.[26] However, this has not been fully tested in clinical trials,[27,28] leading to specu-

Table 2: Exudative recurrences in eyes during the extension phase of the treat-and-extend regimen with ranibizumab[45]

Exudative recurrence frequency	Eyes (%)
0	42 (45.7)
1	28 (30.4)
2	8 (8.7)
3	5 (5.4)
4	2 (2.2)
Persistent exudation	7 (7.6)

Table 3: Vision and CRT outcomes In the Australian prospective open-label treat-and-extend trial

	Baseline	3 months	12 months	Change from baseline at 12 months
Mean BCVA • logMAR • Snellen equivalent	 0.49 (0.39–0.58) 20/62	 0.34 (0.24–0.44) 20/44	 0.36 (0.26–0.46) 20/46	 –0.13 (P = 0.008) +1.3 lines (+7 letters)
Mean CRT, mm	330.9 (307.0–354.8)	244.3 (212.0–254.0)	266.3 (248.0–284.6)	266.3 (248.0–284.6)

BCVA = best-corrected visual acuity; MAR = minimum angle of resolution

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lation that the highly variable characteristics of the disease play an important role in influencing how the individual patient will respond to the treatment. In addition, individual variations among AMD patients (ie, time to steady-state concentration, differences in drug clearance, and blood vessel growth) may have a significant impact on the frequency of intravitreal anti-VEGF treatments required for effective management of any individual patient. Several animal studies revealed the enhanced clearance of VEGF post-vitrectomy.[29,30] In human studies with bevacizumab, vitrectomized eyes had worse VA and central retinal thickness outcomes compared with nonvitrectomized eyes.[31,32]

Lessons Learned From Anti-VEGF Trials

Several Phase III randomized clinical trials (ANCHOR,[33] MARINA,[34] CATT,[35] and VIEW 1–2[27,28]) have shown that monthly intravitreal injections of ranibizumab 0.5 mg improve visual and anatomical outcomes in patients with wet AMD, as assessed over a treatment period of 1 or 2 years. The most important predictors of improvement in VA, as demonstrated by a subgroup analysis of the MARINA and ANCHOR trials, were baseline best-corrected visual acuity (BCVA) score, CNV lesion size, and age.[36,37]

The possibility of quarterly ranibizumab administration was evaluated in the PIER (N=184)[38] and EXCITE (N=353)[39] trials. Although the overall results from both trials indicated that quarterly injections were insufficient to maintain the initial VA gain, *post hoc* analysis of the PIER trial identified a proportion of patients who maintained the initial VA benefit throughout the study (Figure 1).

To date, the CATT trial provides the best evidence in support of ranibizumab as-needed (PRN) dosing.[35] Over a 1-year period, the mean BCVA gain (6.8 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) was equivalent to that with monthly dosing (8.5 letters), but was achieved with significantly fewer injections (6.9 versus 13). However, to provide visual outcomes comparable to monthly treatment, the PRN regimen requires monthly monitoring to determine the need for retreatment as well as the use of optical coherence tomography (OCT) to guide retreatment. Thus, although the number (and cost) of injections can be reduced with PRN compared to the monthly regimen, the number of monthly visits (and the burden on patients and their caregivers) remains the same.

The SAILOR trial further confirmed that the success of PRN treatment depends on monthly monitoring.[40] During the loading phase of this trial when patients were monitored and treated every month, mean BCVA increased. However, once patients entered the maintenance phase, where they were monitored and treated (if needed) every 3 months, the BCVA decreased. This highlights the fact that quarterly visits are insufficient to detect disease progression and reinitiate treatment in a timely manner. According to a preliminary report of the HARBOR trial (a large [N=1097] randomized double-masked multicentre Phase III trial), the mean BCVA gain over 1 year with PRN dosing (8.2 ETDRS letters) did not achieve non-inferiority (margin of ±4 letters) to that with monthly dosing (10.1 letters).[41]

Although all of the abovementioned studies suggest numerically better outcomes with monthly dosing, they also indicate that monthly treatment may not be necessary for all patients. The PrONTO study was the first attempt to assess individualized ranibizumab treatment.[42] It was a 2-year prospective trial that enrolled 40 AMD patients with subfoveal CNV (VA between 20/40 and 20/400 and a central retinal thickening [CRT] of ≥300 µm). Patients received 3 consecutive monthly intravitreal injections of ranibizumab and were retreated based on the criteria presented in Table 1. At the 1-year follow-up, the mean VA improvement was 9.3 letters with 35% of patients showing an improvement of ≥15 letters. These visual outcomes were similar to those achieved in the MARINA and ANCHOR trials but the number of required injections was significantly lower: 5.6 injections over 12 months. Exudative recurrence, however, was noted in 37 (92.5%) of the 40 eyes in the study. In addition to showing that individualized treatment of wet AMD can be very effective, the PrONTO study also established the role of OCT in evaluating the effect of treatment. Although clinical examination and VA are important in evaluating outcomes in patients with wet AMD, they may not be sufficient. For example, as VA can vary, it may not be reflective of disease activity.[42] Furthermore, changes on OCT often precede VA deterioration.[42,43]

The lessons learned from the clinical trials described above led to the consideration of an alternative 'treat-and-extend' approach in daily practice.[44] The strategy is geared toward minimizing the number and cost of injections and clinic visits. The approach includes a loading phase of monthly treatment that is followed by a maintenance phase in which the interval between injections is progressively lengthened or shortened depending on the presence or absence of disease activity.

Table 4: CAN-TREAT: trial objectives

Primary objective:

To sequentially compare the effectiveness of 2 treatment regimens by assessing the mean change in BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) from Baseline to Month 12. If the treat-and-extend regimen is noninferior to the monthly regimen, then superiority of treat-and-extend over monthly treatment will be assessed by the number of injections from baseline to Month 12.

Secondary objectives:

- To evaluate the treatment frequency and duration of treatment-free intervals applied in the treat and extend dosing regimen arm.
- To compare the proportion of patients with a gain of ≥5, ≥10, ≥15 letters between the 2 treatment arms from baseline to Month 12 and from baseline to Month 24.
- To compare the proportion of patients with a loss of <5, <10, <15 letters between the 2 treatment arms from baseline to Month 12 and from baseline to Month 24.
- To compare the mean change in BCVA ETDRS between the 2 treatment arms at Month 12 compared to Month 3.
- To compare the mean change in BCVA ETDRS between the 2 treatment arms from baseline to Month 24.
- To compare the number of injections performed between the 2 treatment arms from baseline to Month 24.
- To compare the number of injections performed between the 2 treatment arms from Month 12 to Month 24.

To date, the only evidence for this dosing regimen comes from retrospective case studies.[45-47] Analyses of the treat-and-extend approach of ranibizumab (92 eyes)[45] and bevacizumab (74 eyes),[46] respectively, showed significant improvements in vision. In both trials, patients receiving the treat-and-extend approach gained 3 lines of vision. The number of injections was also reduced to approximately 8 per year. Nearly one-half of eyes (42 eyes; 45.7%) receiving ranibizumab in this manner demonstrated no exudative recurrence after an exudation-free macula was achieved (Table 2).[45] Furthermore, in a recent prospective, 12-month, open-label, nonrandomized, multicentre, treat-and-extend study conducted in Australia, which followed the PrONTO re-treatment criteria, vision improved by 1.3 lines (P=0.008; Table 3).[47]

Table 5: CAN-TREAT: key inclusion criteria

- Diagnosis of treatment-naive CNV secondary to age-related macular degeneration (AMD) in the study eye, for which ranibizumab has been prescribed by the treating physician. This includes lesions with
  - <50% hemorrhage
  - <50% fibrosis
  - <50% serous pigment epithelial detachment
- BCVA score in the study eye between 78 and 19 letters inclusively, using ETDRS visual acuity charts at a testing distance of 4 m
  - Approximate Snellen equivalent of 20/32 to 20/400 at screening
- Age ≥50 years
- Patients are able to give written informed consent

CAN-TREAT Trial: The Canadian Experience

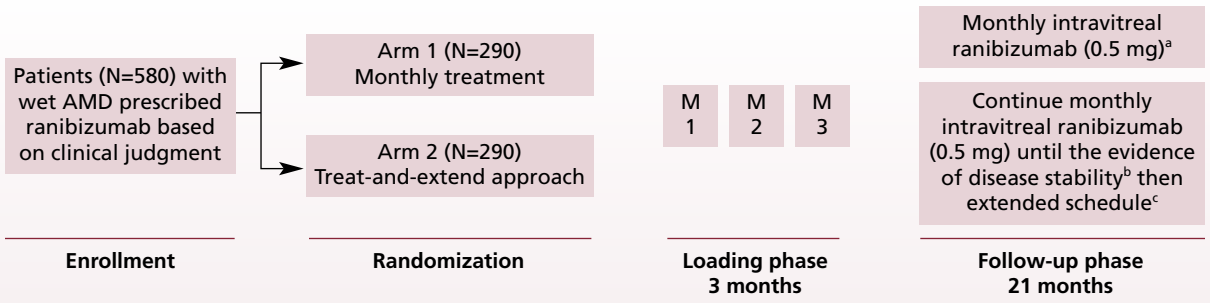
CAN-TREAT (Canadian Treat and Extend Analysis Trial with Ranibizumab) is a multicentre, randomized Canadian trial designed to evaluate and compare the monthly administration of ranibizumab to the treat-and-extend approach in achieving and maintaining a maximum visual function benefit (ie, BCVA stability). The objectives of the trial are listed in Table 4 and the details and schema of the trial design are provided in Figure 2. The trial is expected to enroll a total of 580 patients from 20–25 participating centres. Key inclusion criteria are shown in Table 5. The primary endpoints are the mean change in BCVA and the mean number of injections administered from baseline to Month 12.

It is hypothesized that the treat-and-extend regimen will be noninferior to monthly dosing in terms of mean change in BCVA from baseline to Month 12. To that end, a noninferiority margin of 5 letters was selected, as it represents a clinically meaningful change in vision. It is also expected that the number of injections in the treat-and-extend regimen will be significantly lower than the number of injections in the monthly dosing regimen from baseline to Month 12. It is assumed that the treat-and-extend regimen is "superior" to the monthly dosing regimen if the decrease in mean number of injection between the 2 groups is at least 2 at month 12. Overall, it is anticipated that the treat-and-extend approach will allow for proactive, individualized treatment as opposed to PRN reactive, treatment.

Conclusion

The value of the CAN-TREAT trial is that it is the first randomized, multicentre trial that compares the efficacy of monthly anti-VEGF injections to the treat-and-extend approach in maximizing VA in AMD patients. The trial will also assess the relationship between patient-specific charac-

Figure 2: CAN-TREAT: trial design



Follow-up visits assessments: Month 12/Week 52 and Month 24/Week 104.

[a] Monthly arm will undergo ophthalmic examinations, BCVA ETDRS assessments and OCT every 3 months

[b] Disease stability = A gain in visual acuity of <3 ETDRS letters from the prior month, no clinical evidence of lesion growth, fluid or blood, and no intraretinal or subretinal fluid on OCT

[c] Extended schedule = The intervals between each subsequent injection will be extended by 2 weeks (intervals of 6 weeks, 8 weeks, 10 weeks, to a maximum of 12 weeks) until clinical or diagnostic evidence of disease instability is observed based on OCT findings and/or BCVA ETDRS.

Disease instability is defined as the presence of any fluid and/or a vision loss of >5 letters, and/or the presence of new hemorrhage or progression of CNV.

In case of clinical or diagnostic evidence of disease instability, the interval period between injections will be shortened from the previous interval (by 2 weeks if the intervals is 6 or 8 weeks, or by 4 weeks if the interval is 10 or 12 weeks) until disease stability is regained. Once stability is regained, the extension of intervals between injections will resume by maintaining the current interval for the next injection and if disease stability is confirmed, then the extended intervals between injections will resume. Should the patient fail during the second attempt to extend at the same interval, no further attempts to extend the patient beyond that point will be made. The last stable interval will be selected as the patient's personalized interval, and this interval will then be maintained throughout the remainder of the study assuming clinical and OCT stability.

teristics and frequency of treatment, and the possibility of preserving vision while reducing the injection burden. By proving the validity of the treat-and-extend approach and answering outstanding treatment related questions, the CAN-TREAT trial will provide an important benchmark for future investigations, therapeutic approaches, and administration strategies.

References:

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ.* 2004;82(11):844-851.
2. Gottlieb JL. Age-related macular degeneration. *JAMA.* 2002;288(18): 2233-2236.
3. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med.* 2008;358(24):2606-2617.
4. Gehrs KM, Anderson DH, Johnson LV, Hageman GS. Age-related macular degeneration – emerging pathogenetic and therapeutic concepts. *Ann Med.* 2006;38(7):450-471.
5. Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ.* 2000;321(7263):741-744.
6. Kliffen M, Sharma HS, Mooy CM, Kerkvliet S, de Jong PT. Increased expression of angiogenic growth factors in age-related maculopathy. *Br J Ophthalmol.* 1997;81(2):154-162.
7. Wells JA, Murthy R, Chibber R, et al. Levels of vascular endothelial growth factor are elevated in the vitreous of patients with subretinal neovascularisation. *Br J Ophthalmol.* 1996;80(4):363-366.
8. Bellan L, Buske L. Ophthalmology human resource projections: are we heading for a crisis in the next 15 years? *Can J Ophthalmol.* 2007; 42(1):34-38.
9. Buhrmann R, Hodge W, Gold D. National and Provincial Estimates of Vision Loss and Age-related Eye Diseases 2006 to 2031. From: Buhrmann R. Foundations for a Canadian Vision Health Strategy. Toronto: National Coalition for Vision Health. 2007. Available at: http://www.visionhealth.ca. Accessed on April 8, 2013.
10. Hassell JB, Lamoureux EL, Keeffe JE. Impact of age related macular degeneration on quality of life. *Br J Ophthalmol.* 2006;90(5):593-596.
11. Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. The psychosocial impact of macular degeneration. *Arch Ophthalmol.* 1998; 116(4):514-520.
12. British Columbia Approves Lucentis Funding for Macular Degeneration. Available at: http://www.amdsupport.ca/2009/04/09/british-columbia-approves-lucentis-funding-for-macular-degeneration. Accessed on April 4, 2013.
13. Province to Fund Lucentis Treatment. Available at: http://www.gov.ns.ca/news/details.asp?id=20101020006. Accessed on April 4, 2013.
14. Cruess A, Maberley D, Wong D, Chen J. The treatment of wet AMD in Canada: access to therapy (policy review). *Can J Ophthalmol.* 2009;44 (5):548-556.
15. Cruess AF, Berger A, Colleaux K, et al. Canadian expert consensus: optimal treatment of neovascular age-related macular degeneration. *Can J Ophthalmol.* 2012;47(3):227-235.
16. Chong V. Biological, preclinical and clinical characteristics of inhibitors of vascular endothelial growth factors. *Ophthalmologica.* 2012;227(Suppl 1):2-10.

17. Yu L, Liang XH, Ferrara N. Comparing protein VEGF inhibitors: In vitro biological studies. *Biochem Biophys Res Commun*. 2011;408(2):276-281.
18. Papadopoulos N, Martin J, Ruan Q. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;15(2):171-85.
19. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Ezzat MK, Singh RJ. Pharmacokinetics of intravitreal ranibizumab (Lucentis). *Ophthalmology.* 2007;114(12): 2179-2182.
20. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology.* 2007;114(5):855-859.
21. Heiduschka P, Fietz H, Hofmeister S, et al. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. *Invest Ophthalmol Vis Sci.* 2007;48(6):2814-2823.
22. Gaudreault J, Fei D, Beyer JC, et al. Pharmacokinetics and retinal distribution of ranibizumab, a humanized antibody fragment directed against VEGF-A, following intravitreal administration in rabbits. *Retina.* 2007;27(9):1260-1266.
23. IVAN Study Investigators; Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology.* 2012;119(7):1399-1411.
24. Kim H, Robinson SB, Csaky KG. FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye. *Mol Vis.* 2009;15:2803-2812
25. Stewart MW. Aflibercept (VEGF Trap-Eye) for the treatment of exudative age-related macular degeneration. *Expert Rev Clin Pharmacol.* 2013;6(2):103-113.
26. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol.* 2008;92(5):667-668.
27. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology.* 2012;119(12):2537-2548.
28. Heier JS, VIEW 1 and VIEW2 Investigators. 96 Weeks Results from the VIEW 1 and VIEW 2 Studies: Intravitreal Aflibercept Injection versus Ranibizumab for Neovascular AMD Shows Sustained Improvements in Visual Acuity. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale (FL): May 6-9, 2012. Abstract 6962.
29. Lee SS, Ghosn C, Yu Z, et al. Vitreous VEGF clearance is increased after vitrectomy. *Invest Ophthalmol Vis Sci.* 2009;51(4):2135-2138.
30. Kakinoki M, Miyake T, Sawada O, Sawada T, Kawamura H, Ohji M. The clearance of intravitreal bevacizumab in vitrectomized macaque eyes. Poster presented at the ARVO Annual Meeting. Fort Lauderdale (FL); May 5, 2011.
31. Mehta S, Blinder KJ, Shah GK, Kymes SM, Schlief SL, Grand MG. Intravitreal bevacizumab for the treatment of refractory diabetic macular edema. *Ophthalmic Surg Lasers Imaging.* 2010;41(3):323-329.
32. Yanyali A, Aytug B, Horozoglu F, Nohutcu AF. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. *Am J Ophthalmol.* 2007;144(1):124-126.
33. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology.* 2009;116(1):57-65.
34. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006; 355(14):1419-1431.
35. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two year results. *Ophthalmology.* 2012;119(7):1388-1398.
36. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. *Am J Ophthalmol.* 2007;144(6):850–857.
37. Boyer DS, Antoszyk AN, Awh CC, et al. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology.* 2007;114(2):246–252.
38. Regillo CD, Brown DM, Abraham P, et al. Randomized, double- masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol* 2008;145:239–248.
39. Bolz M, Schmidt-Erfurth U. Ranibizumab EXCITE study: Exploring the value of optical coherence tomography for the management of ranibizumab therapy in age-related macular degeneration. Paper presented at: 8th Euretina Congress; May 22, 2008; Vienna, Austria.
40. Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. *Ophthalmology.* 2009;116(9):1731-1739.
41. Suner IJ, Yau L, Lai P. HARBOR study: one-year results of efficacy and safety of 2.0 mg versus 0.5 mg ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration [abstract no. 3677]. Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale; May 6–10 2011.
42. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007; 143(4):566-583.
43. Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. *Am J Ophthalmol* 2007;144:627–637.
44. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. *Am J Ophthalmol* 2007;143: 679–680.
45. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;117:2134–2140.
46. Shienbaum G, Gupta OP, Fecarotta C, et al. Bevacizumab for neovascular age-related macular degeneration using a treat and- extend regimen: clinical and economic impact. *Am J Ophthalmol* 2011;153:468–473.
47. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. *Retina.* 2013 Mar 27. [Epub ahead of print]

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