

Treat and Extend: A Better Approach to Individualized Dosing for Wet AMD?

This strategy can lower the frequency of injections and the costs and anti-VEGF therapy.

BY OMESH P. GUPTA, MD, MBA

Two phase 3 clinical trials, MARINA and ANCHOR, demonstrated a treatment advantage of approximately 20 letters on the Early Treatment Diabetic Retinopathy Study scale for ranibizumab (Lucentis, Genentech) in comparison with sham treatment and photodynamic therapy, respectively. The majority of retina clinicians, however, do not practice the same protocol used in MARINA and ANCHOR—one injection every 4 weeks—according to the results of the 2009 American Society of Retina Specialists (ASRS) Preferences and Trends Survey. In this survey, 92% of respondents reported treating their patients with neovascular age-related macular degeneration (AMD) in an individualized fashion.¹ These approaches appear to be more convenient and cost-effective for patients, may yield fewer risks associated with injections, and have the potential to minimize systemic adverse events.

Currently, there are two main strategies for individualized treatment of neovascular AMD. Patients can receive injections as needed upon signs of recurrent exudation (treat and observe), or a treat-and-extend strategy can be used, in which the intervals between treatments are extended as long as the macula remains dry. Treat and extend is a term that was coined by K. Bailey Freund, MD, who published the first reports on this strategy.^{2,3} In the 2009 ASRS survey, 56% of physicians reported employing treat-and-observe and 44% reported employing treat-and-extend for their patients with neovascular AMD.¹

TREAT AND EXTEND

In studies evaluating ranibizumab as needed with similar

follow-up periods, the best visual outcome of a 7.3-letter gain was achieved with the most injections, and the poorest outcome was a 0.7 letter gain with the fewest injections.⁴⁻⁶

A recent retrospective study (n=90) compared as-needed dosing with treat-and-extend dosing over 1 year.⁷ In this study, 52 eyes were in the as-needed arm and 38 were in the treat-and-extend arm. At 1 year, the eyes in the as-needed arm gained 2.3 (± 17.4) ETDRS letters, while eyes in the treat-and-extend arm gained 10.8 (± 8.8) ETDRS letters ($P=.036$). The number of injections was statistically significantly higher in the treat-and-extend arm at 7.8 (± 1.3) compared with 5.2 (± 1.9) in the as-needed arm ($P<.001$).

RETROSPECTIVE STUDY FOR TREAT AND EXTEND

Along with colleagues, I conducted a retrospective study of 166 eyes of 159 patients to evaluate the visual outcome, number of injections, and direct medical costs of a treat-and-extend regimen to manage neovascular AMD with ranibizumab (n=92) or bevacizumab (n=74; Avastin, Genentech).⁸ We included only treatment-naïve patients with a minimum follow-up of 6 months (mean follow up of 1.5 years). All types of choroidal neovascularization lesions were included. The baseline characteristics of our cohort were similar to those in the MARINA, ANCHOR, and PrONTO trial in terms of sex, age, race, entry visual acuity, and size of lesion.

For the visual acuity endpoint, fluorescein angiography (FA) and optical coherence tomography (OCT) images were obtained, and Snellen visual acuities were converted

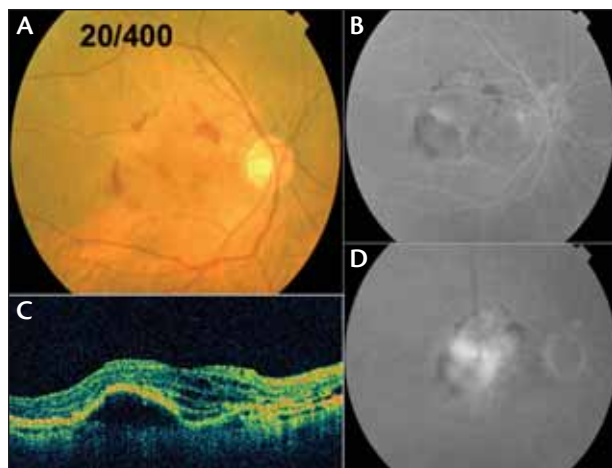


Figure 1. Patient managed with treat-and-extend strategy. Baseline visual acuity of 20/400.

to ETDRS letter scores using a method described by Gregori et al.⁹

For the cost comparisons to MARINA, ANCHOR, and PrONTO, we included the costs of the clinical exam, FA, OCT, and the associated costs of ranibizumab and bevacizumab.

Patients received monthly injections of ranibizumab or bevacizumab until the macula was dry on OCT, when the intervals between visits were extended by 2 weeks unless there were signs of recurring exudation. Upon signs of recurring exudation (intraretinal or subretinal fluid or new macular hemorrhage), the interval was shortened by

2 weeks. At 12 weeks, patients could decide either to go under observation or continue with treatment.

OVERALL OUTCOMES

In the group receiving ranibizumab injections, the mean gain at 2 years was 9.7 ETDRS letters. The visual acuity gains for those receiving bevacizumab were similar at 2 years: 10 ETDRS letters. The percentage of three-line gainers, those who were stable throughout, and those who lost more than three lines of visual acuity were also similar between the groups. Patients treated with ranibizumab could be extended on average 80 days and those treated with bevacizumab could be extended on average 90 days, which was not a statistically significant difference in this small cohort of patients. The mean number of injections over the first year was fairly similar: 8.36 in the ranibizumab arm and 7.94 in the bevacizumab arm. The mean number of injections after the first year, however, was statistically significantly greater in the ranibizumab arm (7.45) compared with the bevacizumab arm (5.6). In terms of exudative recurrence, approximately 45% to 52% of patients had no recurrence over the course of the study. Approximately 30% of patients in either arm had one recurrence. Approximately 7% of patients in either arm had persistent exudation despite monthly injections.

In regard to cost, the mean annual costs for ranibizumab were calculated to be \$28,314 in MARINA and ANCHOR and \$15,880 in the PrONTO study. For the first year of our treat-and-extend study, the mean cost for

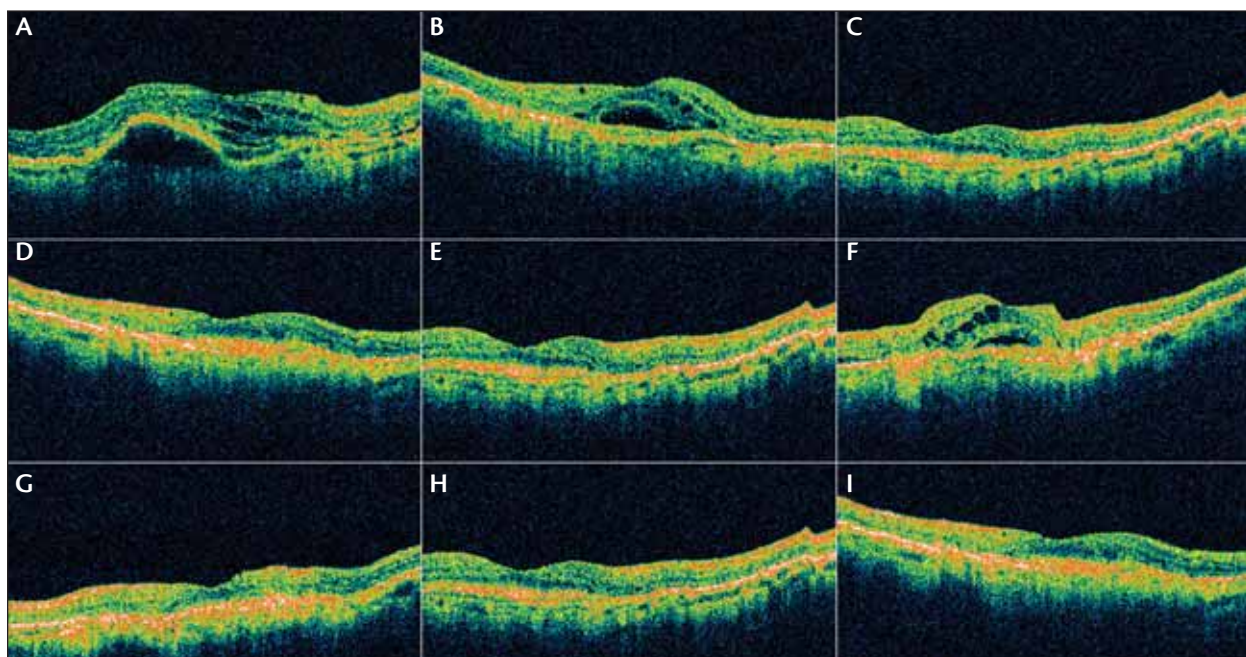


Figure 2. OCT images during the course of the treat-and-extend regimen (A-I). The ninth ranibizumab injection (I) resulted in an increase of visual acuity to 20/30 and stable foveal retinal thickness.

ranibizumab was \$16,114 compared with \$3,734 for bevacizumab. Between year 1 and year 2, the costs for ranibizumab dropped to approximately \$14,000 while the costs for bevacizumab dropped to approximately \$1,800.

CASE EXAMPLE

One of our patients had 20/400 vision at baseline; fluorescein and OCT images are shown in Figure 1. After three injections of ranibizumab the macula was dry (Figure 2). The intervals between treatments were extended to 6 weeks, 8 weeks, and 10 weeks. After the 10-week visit, there was some recurrence of exudation, so the patient was injected and the interval was shortened to 8 weeks. The patient was then re-challenged once dry, and the interval was extended first to 10 weeks and then to 12 weeks. Since that time, the patient has been receiving quarterly injections with an ultimate visual acuity of 20/40.

CONCLUSION

We have found that a treat-and-extend regimen using ranibizumab or bevacizumab is associated with significant visual improvement from baseline. This strategy is also associated with fewer patient visits, fewer injections, and a lower direct annual medical cost compared with costs calculated for the phase 3 clinical trials of ranibizumab. Additionally, significant cost savings can be achieved by using bevacizumab as an alternative to ranibizumab. ■

Omesh P. Gupta, MD, MBA, is an Assistant Professor of Clinical Ophthalmology at Temple University School of Medicine in Philadelphia. He states that he has no financial relationships to disclose. Dr. Gupta may be reached at +1 215 707 3185; or via e-mail at ogupta@hotmail.com.



1. American Society of Retina Specialists Annual Preferences and Trends Survey, 2009. <http://www.asrs.org>; access for members only.
2. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified "treat and extend" dosing regimen of intravitreal anti-vascular endothelial growth factor therapy. *Retina*. 2010;30(9):1368-1375.
3. Engelbert M, Zweifel SA, Freund KB. "Treat and extend" dosing of intravitreal anti-vascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. *Retina*. 2009;29(10):1424-1431.
4. Rothenbuehler SP, Waerber D, Brinkmann CK, Wolf S, Wolf-Schnurbusch UE. Effects of ranibizumab in patients with subfoveal choroidal neovascularization attributable to age-related macular degeneration. *Am J Ophthalmol*. 2009;147(5):831-837.
5. Dadgostar H, Ventura AA, Chung JY, Sharma S, Kaiser PK. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology*. 2009;116(9):1740-1747.
6. Cohen SY, Dubois L, Tadayoni R, et al. Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. *Am J Ophthalmol*. 2009 Sep;148(3):409-413.
7. Oubrahim H, Cohen SY, Samimi S, et al. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. *Retina*. 2011;31(1):26-30.
8. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration: clinical and economic impact. *Ophthalmology*. 2010;117(11):2134-2140.
9. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina*. 2010;30(7):1046-1050.