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. 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. 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.

**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.

A recent retrospective study (n=90) compared as-needed dosing with treat-and-extend dosing over 1 year. 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). We included only treatment-naive 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...
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
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.

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