

Real-World Dosing Strategies for Ranibizumab

Landmark trials have changed the way neovascular AMD is managed; however, the administration schedule used in the trials places a burden on patients, subspecialists, and the entities that pay for health care.

BY PHILIP J. ROSENFELD, MD, PhD

Two phase 3, multicenter, controlled clinical trials have demonstrated the efficacy of a monthly injection of 0.5-mg ranibizumab (Lucentis; Genentech, San Francisco) for the treatment of neovascular age-related macular degeneration (AMD).^{1,2} Not only did the monthly injection regimen prevent significant vision loss in 95% of patients in these two trials, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR), it also improved visual acuity in most patients in the trials. As many as 40% of patients in the two trials improved by three lines of visual acuity or more at the 2-year follow-up point.

LESS-FREQUENT DOSING

Although these landmark trials have changed the way neovascular AMD is managed (Figure 1), the monthly administration schedule used in the trials, when translated to clinical practice, places a significant burden on patients, on retina subspecialists, and on the entities that pay for health care.

For these reasons and others, less-frequent dosing strategies have been and continue to be investigated.

In the Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration (PIER) study,³ in which patients received

TAILORED TREATMENT STRATEGIES FOR RANIBIZUMAB

Strategy 1

- Treat patient monthly until no subretinal fluid is visible on OCT.
- Follow patient monthly until subretinal fluid reappears (eg, at 2 months); re-treat at that time.
- Bring patient back for visits just short of that interval (eg, 6 weeks to 7 weeks); re-treat at that time.
- Continue patient visits at that interval, possibly extending the interval over time.

Strategy 2

- Treat patient monthly.
- When patient returns and no fluid is present, give another injection and extend the next visit to 6 weeks to 8 weeks.
- If fluid is present at 6 weeks to 8 weeks, inject and bring patient back at a shorter interval before fluid develops.
- If no fluid is present at 6 weeks to 8 weeks, give another injection and bring patient back at 8 weeks to 12 weeks.
- Continue to lengthen follow-up interval until fluid is detected and the proper interval for this patient is found.
- Continue to inject at that predefined interval and then consider extending the interval over time.

injections every 3 months after an initial course of three monthly injections, visual acuity improved on average in the first 3 months but then returned to baseline by the 12-month follow-up point. (This out-

come may seem disappointing in comparison to the results of the ANCHOR and MARINA trials, but it still represents an improvement over the natural history of AMD and over previous outcomes with verteporfin [Visudyne, Novartis, East Hanover, NJ] photodynamic therapy and with pegaptanib sodium [Macugen, OSI/Eyetech and Pfizer, both in New York, NY]. In the control arm of the study, patients receiving sham treatment lost an average of 16 lines of visual acuity.)

PrONTO investigated the use of an as-needed or p.r.n. dosing schedule for ranibizumab after three consecutive monthly doses.

At the Bascom Palmer Eye Institute, Genentech funded an investigator-sponsored trial called PrONTO (Prospective Optical Coherence Tomography OCT Imaging of Patients With Neovascular Age-Related Macular Degeneration Treated With Intra-Ocular Lucentis), which investigated the use of an as-needed or p.r.n. dosing schedule for ranibizumab after three consecutive monthly doses. Patients are seen monthly, and retreatment decisions are guided mainly by visual acuity and optical coherence tomography (OCT); retreatment is performed if neovascular activity is seen on monthly OCT or fluorescein angiography performed every 3 months.

RESULTS SIMILAR WITH FEWER TREATMENTS

In the recently published 1-year results of PrONTO,⁴ the mean visual improvement among patients in the study was nine letters, which is comparable to the mean 7.2 letters of improvement seen at 2 years with monthly dosing in the MARINA study and the 10 letters of improvement seen in the ANCHOR trial. The mean number of treatments per patient administered over the course of the year was 5.5, rather than the 13 monthly treatments dictated by MARINA and ANCHOR over the same time period. These results suggest that p.r.n. dosing with ranibizumab can reduce the number of treatments needed while still providing the same or nearly the same level of visual improvement as monthly dosing.

The 2-year results of the PrONTO study have recently been announced,⁵ but they have not yet been published. In the 37 patients who completed the 2-year follow-up in the PrONTO study, the average number

of treatments per year was five, with an average of 9.9 total injections over the 2 years of the study. Mean improvement in visual acuity score was 10.7 letters, with a mean reduction in central retinal thickness on OCT of 215 μm . Baseline vision was maintained by 78% of patients and improved by 15 letters or more in 43% of patients.

The design of the PrONTO study, however, still requires monthly visits that include OCT evaluation. So, although the expense and risk of ranibizumab administration may be saved by the p.r.n. dosing schedule, the time burden on patients and practitioners is not reduced by this strategy.

REAL-WORLD APPROACH

There is no one dosing strategy for ranibizumab that will be acceptable to all doctors and all patients. If a clinician believes that patients must always be treated based on phase 3 clinical trial data, then he or she is obligated to give the patient monthly doses, as was done in MARINA and ANCHOR, or to follow the monthly evaluation schedule in the PrONTO protocol.

On the other hand, clinicians who believe that clinical trial protocols are designed to prove the safety and efficacy of a drug, not necessarily to dictate how patients should be treated in a real-world setting, may instead use clinical trials as guidance on how best to manage their patients. That is my current approach to this issue.

How does one derive a practical approach to evaluation and treatment from the evidence of the clinical trials? From the two extremes of the completed trials—monthly dosing in ANCHOR and MARINA, and every-three-month dosing in PIER—can we arrive at a middle ground that is efficacious and not as demanding on our patients and our practices?

SOME PATIENTS NEED MORE FREQUENT TREATMENT THAN OTHERS

We learned from the PrONTO study that some patients need frequent treatment and some do not. To make the best use of resources, it makes sense to tailor the treatment schedule to the needs of the patient. At Bascom Palmer Eye Institute, we have developed several strategies for retreating patients with a reduced number of patient visits, based on the reappearance of subretinal fluid on OCT (see sidebar, Tailored Treatment Strategies for Ranibizumab). The proper strategy is chosen based on the patient's needs and his or her ability to attend follow-up visits. We have found the results with these strategies

encouraging with the use of both ranibizumab and off-label bevacizumab (Avastin; Genentech).

One strategy is to treat the patient monthly until there is no subretinal fluid visible on OCT; then the patient is followed monthly until fluid reappears in the macula, at which time retreatment is carried out. Once we know the interval at which fluid reappears—say for example 2 months—then we can bring the patient back for subsequent treatment just before we would expect fluid to reappear—in this example at 6 or 7 weeks after the last treatment. We then continue to bring the patient back at that interval, perhaps lengthening the interval after a few treatments to see if it can be safely extended.

Another strategy is to treat the patient monthly until no subretinal fluid is visible on OCT, then give the patient one more monthly treatment even though no fluid has reappeared. When we know the patient can go 1 month without fluid reaccumulating, we then extend the next visit to 2 months and treat—again, treating whether fluid is visible or not. If fluid is visible after 2 months, subsequent visits are scheduled at 6- or 7-week intervals, as in the strategy described. If no fluid is visible at 2 months, the patient is next brought back and treated after 3

With a treat-and-extend strategy, some patients may be given treatments before they truly need them, but it saves the patient from having to come back monthly.

months. In this way, the treatment interval can be lengthened each time until the proper interval is found. With this treat-and-extend strategy, it may be that patients are given some treatments before they truly need them, but it still saves the patient from having to come back monthly for monitoring.

TWO MAIN STRATEGIES

These, then, are our two main treatment strategy alternatives to the monthly treatments used in the clinical trials: Treat until the patient is dry and then follow up on a monthly basis until the proper interval is found, or treat even when the macula is dry and extend the follow-up interval until the proper interval is found.⁶

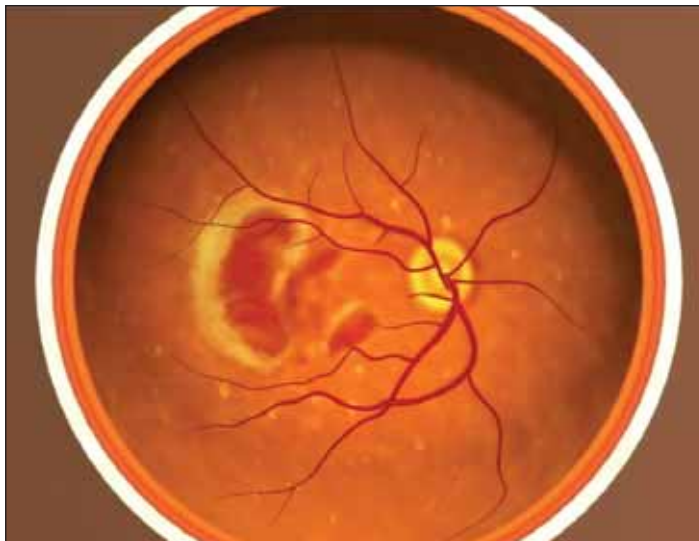


Figure 1. Representation of neovascular AMD.

Image courtesy of NEI

In theory, these treatments should be evaluated in further clinical trials, but even though our experience with them to date has been encouraging, it is unlikely that resources will be available to test both methods. Realistically, it seems likely that visual acuity results will fall somewhere between those in the MARINA and ANCHOR studies and those in the PIER study, with results closer to the two phase 3 trials. For this reason, it seems likely that our clinical judgment will determine how best to treat our patients. ■

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