

Anti-VEGF Maintenance Therapy for Neovascular AMD

Several protocols to reduce the treatment burden associated with intravitreal anti-VEGF injections are under investigation.

BY CARL D. REGILLO, MD

Current management of neovascular age-related macular degeneration (AMD) involves the use of pan-VEGF-blocking drugs to control signs of exudation. Three drugs—ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and bevacizumab (Avastin, Genentech)—injected intravitreally work well to achieve relatively quick resolution of exudative signs in most patients.

Drying of the exudative or “wet” macula in neovascular AMD can usually be accomplished safely, effectively, and relatively quickly with an initial series of frequent, continuous therapy with 1 of these drugs in the so-called induction phase. In most patients, the signs of exudation are brought under good control within 3 to 4 injections in this phase (Figure 1).

For the most part, the induction phase is a straightforward process, and it has been more or less uniformly adopted by clinicians worldwide. It is what to do thereafter, how to keep the macula dry and obtain the best visual outcome in the long run—the maintenance phase—that is the challenge and where clinicians’ practices can vary considerably.

Several factors must be kept in mind when choosing the approach to maintenance therapy for wet AMD. First, these drugs do not cure or change the course of wet AMD, so ongoing therapy is likely to be needed for many years in most patients. Second, the optimal

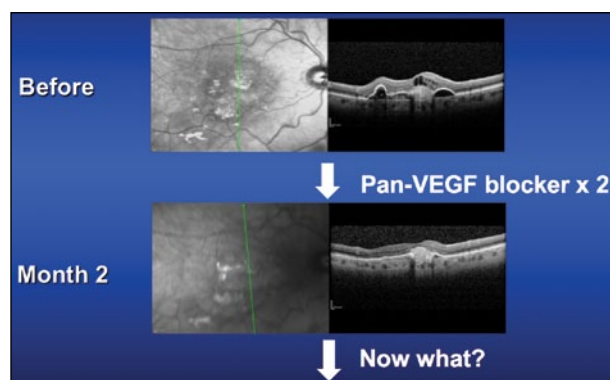


Figure 1. A typical induction phase response with resolution of the exudation as seen on optical coherence tomography (OCT) imaging after 2 monthly intravitreal injections of a pan-VEGF inhibitor.

treatment regimen is not known, and the best management approach may be different for each patient. Third, as with any medical treatment, the best course of therapy for a given patient includes consideration of efficacy, safety, and treatment burden.

FIXED AND VARIABLE REGIMENS

There are 3 basic approaches to maintenance dosing regimens, 2 of which are individualized.

The first is a fixed, continuous, monthly or bimonthly

injection schedule, as was used in the pivotal clinical studies of the anti-VEGF drugs. The second is an individualized discontinuous-variable approach, also called *as-needed* or *pro re nata* (PRN) dosing. The third is an individualized continuous-variable approach, commonly known as a *treat-and-extend* (TAE) strategy.

Although the initial clinical trials of ranibizumab were conducted with fixed-continuous dosing schedules, in clinical practice this type of schedule was never widely adopted because of the burden it placed on patients, practices, and the health care system. Fairly early in the experience with anti-VEGF therapy, clinicians began to utilize PRN dosing. More recently, there has been a strong trend toward the use of the TAE strategy, especially in the United States. The 2013 Preferences and Trends survey by the American Society of Retina Specialists found that 78% of respondents routinely use the TAE approach to maintenance therapy, up from 67% in 2012. During the same time period, use of PRN dosing declined from 24% to 16% of respondents, and fixed dosing from 9% to 3%.¹

Fixed-Continuous

Level 1 evidence from prospective, randomized, clinical studies has demonstrated that the 3 available anti-VEGF drugs are efficacious and safe for the management of wet AMD when used in a fixed-continuous dosing regimen.²⁻⁸ Therefore, why not treat everyone in a fixed monthly or bimonthly fashion? There are a number of reasons. Wet AMD is a heterogeneous disease with a variable natural history, and patients have a variable treatment response to anti-VEGF drugs. It is known that many patients do well without monthly treatment. And finally, recent research has shown that VEGF suppression varies among patients.

Regarding that last point, Muether and colleagues demonstrated several important concepts in studies of aqueous VEGF concentrations before injections in eyes receiving ranibizumab therapy for wet AMD.^{9,10} First, they showed that VEGF suppression correlated with clinical response, or rather that lack of VEGF suppression correlated with recurrence of exudation. Second, they found that the mean interval of VEGF suppression was between 36 and 38 days, but with a wide range—as little as 26 and as great as 69 days. Third, they found that, for a given patient, there seems to be a stable pattern of VEGF suppression for up to 3 years.

With this analysis as a backdrop, it is informative to look at the distribution of treatments given in the HARBOR study.¹¹ In this phase 3 study, 0.5-mg and 2.0-mg injections of ranibizumab were given on a monthly or PRN basis. While the 2-year results of this study have

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not been published, they have been presented.¹² Without going into too much detail, it can be said that the median number of 0.5 mg ranibizumab injections given on a PRN basis in patients who completed the 2-year study was 14.0, and the range, again, was wide, with patients receiving as few as 3—the mandated minimum number of injections—and as many as 24 over the 2 years. The range of injection frequency illustrates the great heterogeneity of patients' responses to anti-VEGF therapy.

This analysis suggests that if all patients were treated on a monthly regimen, many patients would be overtreated. The results of overtreatment include extra expense in both direct and indirect costs, less convenience for patients burdened with frequent visits, and increased cumulative risk. With chronic injections, these risks include endophthalmitis, glaucoma, possible atrophy exacerbation,¹³ and systemic side effects.

Variable-Discontinuous

The possibility of overtreatment and the reality of treatment burden with a fixed schedule led to interest in the use of individualized therapy with PRN dosing. The advantages of PRN dosing over a fixed regimen include less frequent injections (although not necessarily less frequent visits and testing), greater safety, more cost-effective management, and the ability to identify the rare patient who may not need ongoing treatment.

Examination of PRN anti-VEGF dosing started with the PrONTO study,¹⁴ a small, prospective, uncontrolled investigator-sponsored trial with 40 patients. Visual results were comparable with those of the pivotal phase 3 trials of ranibizumab, with a good therapeutic effect sustained over 2 years and reduced treatment frequency: a mean 5.6 injections in the first year and 4.3 in the second year.

Results in the larger, prospective SAILOR trial¹⁵ were not as good, with a decline in mean visual acuity (VA) over time. However, in this study, patients were not followed very frequently. The protocol mandated only quarterly visits, and patients received a mean of 4.9 treatments

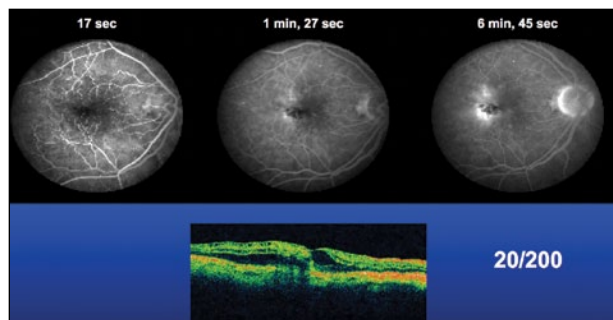


Figure 2. PRN treatment, baseline. Pretreatment fluorescein angiogram (FA) and corresponding OCT of a patient with new signs of wet AMD and decreased VA with subfoveal occult choroidal neovascularization and overlying macular edema in the right eye.

over 9 visits. It is likely, therefore, that many patients were undertreated in this study.

The PRN approach carries certain potential limitations. It may allow recurrence of neovascularization and leakage, and multiple recurrences over time have the potential to lead to progression of disease from which the patient may not fully recover. This in turn can lead to poorer long-term visual outcomes in some patients (Figures 2 and 3).

The fact that certain patients need frequent injections could explain declines in long-term results with PRN dosing in certain studies. At 1 year in CATT, for example, the VA results in the fixed monthly and PRN arms were similar with both ranibizumab and bevacizumab, with differences of only 1.7 and 2.1 letters between fixed and PRN dosing, respectively.⁵ By 2 years, the differences between fixed and PRN arms were greater, and statistically at 2 years the pooled PRN arms were not noninferior to monthly treatment arms.⁶

Furthermore, after 1 year in CATT, the monthly arms were rerandomized, with some patients receiving continued monthly dosing and some switched to PRN dosing. Despite receiving 12 monthly injections in year 1, by the end of year 2 the results in patients crossed over to PRN dosing were similar to those of patients who had PRN dosing from the beginning of the trial. This was seen with both drugs.⁶

In the VIEW studies, in which all arms received PRN dosing in year 2, the results were good for all arms, but again there was a trend toward decline. Whereas VA improvement from baseline ranged from 8.3 to 9.3 letters at year 1, by year 2 the gain from baseline was 6.6 to 7.9 letters.⁴

In IVAN, a European study similar to CATT, the results at year 1 were similarly good with continuous versus PRN therapy, but by year 2 the PRN arms were not noninferior

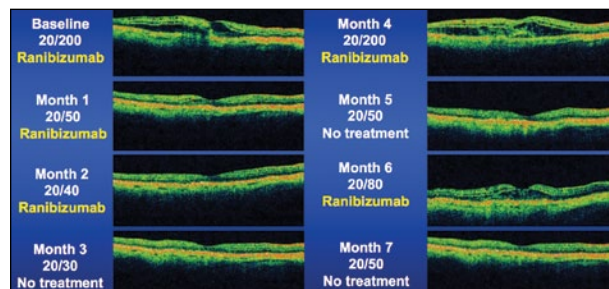


Figure 3. Same eye as Figure 2. Three monthly ranibizumab injections were given with good effect. At month 3, approximately 1 month after the third ranibizumab injection, the macula was free of exudative signs and VA improved from 20/200 to 20/30. The patient was followed monthly, and a PRN therapeutic approach was utilized. Treatment was rendered upon any signs of recurrent exudation on OCT testing. This patient exhibited a high need for anti-VEGF therapy, with a recurrence every time a treatment was skipped. By the end of 7 months of follow-up over 8 visits, there had been a total of 5 treatments and 2 recurrences, and vision had not returned to the best level achieved at month 3.

to continuous therapy.

The HARBOR study provides somewhat of an exception to this trend. Although in HARBOR the VA results in the PRN arms were not as good as those in the monthly arms, these are probably the best PRN results that have been reported. This is the most recently conducted large-scale PRN study, and the only one in which spectral-domain (SD) OCT was used, which may have made a difference in the results. There was a loss of VA from year 1 to year 2 in the 0.5-mg ranibizumab PRN arm, but it was only -0.3 letters,¹⁶ and, by the end of the study, the PRN and monthly 0.5 mg ranibizumab arms differed by only 1.2 letters.

Variable-Continuous

The TAE dosing strategy is continuous dosing with the aims of minimizing recurrences and maximizing long-term visual outcomes. At the same time, dosing is variable, and, therefore, individualized, with the potential to minimize overtreatment, minimize burden, and maximize safety. The variable strategy is also cost-effective, because it minimizes the number of office visits, tests, and injections (Figures 4-6).

Spaide and Freund were the first to describe a TAE regimen,¹⁷ and their group subsequently published two small retrospective series showing good VA outcomes with new-onset wet AMD. Patients were followed for up to 3 years, averaging 6 to 7 treatments yearly with a mean improvement of 4 lines of visual acuity. However, these series included only patients with specific

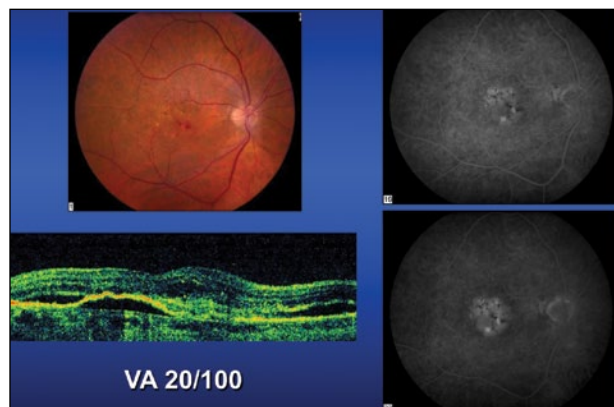


Figure 4. TAE treatment, baseline. Pretreatment fundus photograph, FA, and corresponding OCT of a patient with new signs of wet AMD and decreased VA with subfoveal occult choroidal neovascularization and overlying macular edema, subretinal fluid, and pigment epithelial detachment in the right eye.

neovascularization subtypes, and each study had fewer than 20 patients.^{18,19}

Two larger retrospective studies described the experience of early adopters of the TAE strategy at Wills Eye Hospital.^{20,21} Included were consecutive eyes with new-onset wet AMD receiving ranibizumab ($n = 92$) or bevacizumab ($n = 74$) with a mean follow-up of 1.5 years (minimum 6 months). The mean number of treatments with the 2 drugs was 8.3 and 7.3, respectively, in the first year. The visual results were comparable to those seen in the pivotal studies, with 2.0 and 2.5 lines of VA improvement from baseline, respectively, and approximately a third of patients gaining 3 or more lines.

Investigators in France published a retrospective analysis comparing consecutive patients treated with PRN ($n = 52$) and TAE ($n = 38$) strategies.²² At 1 year, patients treated PRN gained a mean 2.3 letters with 5.2 treatments, and those treated with TAE gained a mean 10.8 letters with 7.8 treatments. A prospective nonrandomized study by investigators in Australia evaluated 1-year results with TAE ranibizumab in 45 patients.²³ After 3 monthly induction doses, mean VA improved 1.3 lines, and 26% of patients gained 3 or more lines of VA with a mean of 8 injections.

Finally, the top line results of the LUCAS study were presented last year at the American Academy of Ophthalmology Annual Meeting.²⁴ This prospective, large-scale study ($n = 432$) compared 1-year results of neovascular AMD treated with either ranibizumab or bevacizumab. Both arms were dosed in a TAE fashion with no induction phase; note that the study did not compare TAE with other treatment regimens. The results with the 2 drugs were found to be equivalent, with a mean VA gain

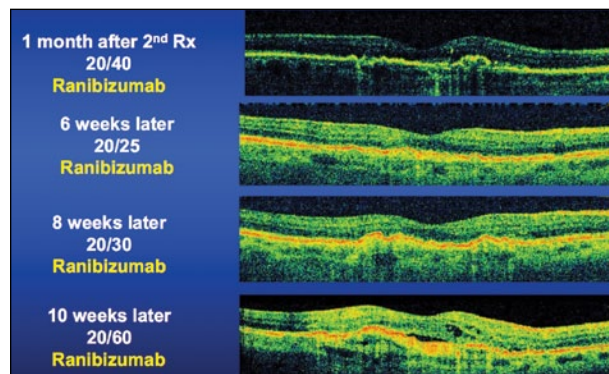


Figure 5. Same eye as Figure 4. Complete resolution of the exudation was achieved after 2 monthly injections of ranibizumab. Treatment and follow-up was extended by 2-week intervals, and a recurrence was first noted with a 10-week extension.

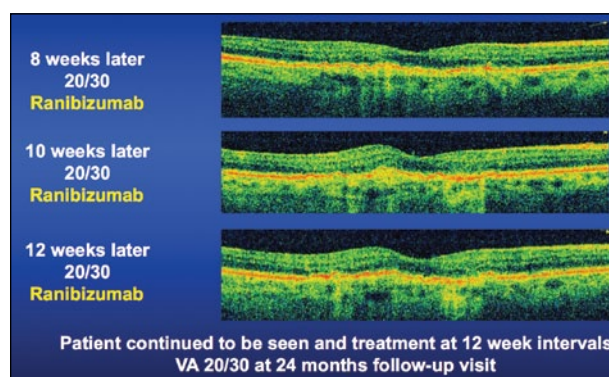


Figure 6. Same eye as Figures 4 and 5. Treatment and follow-up interval was reduced to 8 weeks, and re-extension by 2 weeks followed, with successful extension out to 12 weeks. The patient continued to be seen and treated at 12-week intervals for an additional 24 months with good maintenance of VA and no further signs of recurrent exudation.

of 8.2 and 8.0 letters and a mean of 8.0 and 8.8 treatments, respectively.

The studies described above are currently the sum of the evidence for the efficacy of the TAE treatment approach. There are no clinical studies comparing TAE versus other regimens, but these data are to come. There is unlikely to be a single, definitive study to show how all of these regimens and drugs stack up against each another. However, Wills Eye Hospital is undertaking a small ($n = 40$) uncontrolled prospective investigator-sponsored trial investigating TAE with aflibercept, and the T-REX study by Retina Consultants of Houston is examining monthly versus TAE dosing with ranibizumab. Furthermore, the National Institutes of Health is preparing to launch a larger prospective study comparing PRN

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versus TAE with ranibizumab. Internationally, other TAE studies are being launched or planned.

Many unanswered questions remain regarding how best to use a TAE strategy. How much should the treatment interval be extended at each visit—1, 2, or 4 weeks? Should extension be capped at a certain maximum interval such as 2, 3, or even 4 months? Can or should treatment be discontinued after several months of extension? Should there be a different TAE schedule for aflibercept, which is labeled for a longer treatment interval? Should big recurrences be treated differently from limited, smaller-scale recurrences?

Regardless of the treatment approach chosen, multiple studies point to 1 very important concept, which is no great surprise: Early treatment after early detection, when the neovascular lesion is smaller, leads to better results.^{2,3,11} This is true not only in terms of VA improvement from baseline, but also in absolute VA outcomes.

SUMMARY

There are 3 basic treatment approaches that have been used with anti-VEGF therapy for wet AMD: fixed-continuous, PRN, and TAE. There is insufficient evidence from level 1 studies at this time to determine the best option among these approaches. However, with 78% of retina specialists using TAE, there appears to be a clinical impression that this may be the best compromise among the protocols.

That being said, whatever treatment strategy is chosen for a given patient, the best results will be achieved with early detection and treatment. The aim of treatment should be to minimize the growth of neovascularization and exudation with these well-proven drugs and to preserve the best vision possible for patients over the long term. ■

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