Retinal Physician
Article

Ongoing Treatment for Patients With Neovascular AMD

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Dr. Rosenfeld: Once you decide to initiate anti-vascular endothelial growth factor (anti-VEGF) therapy for a patient with neovascular age-related macular degeneration (AMD), how do you proceed?

Dr. Hariprasad: The randomized controlled clinical trials completed thus far support monthly injections for achieving the best visual outcomes with ranibizumab (Lucentis, Genentech). However, practically speaking, monthly treatment is a tremendous burden for our patients and our practices. Therefore, I treat with ranibizumab monthly until optical coherence tomography (OCT) shows the macula to be completely free of fluid. Some patients reach that point after 2 injections; others require as many as 8 injections. When the macula is dry, I withhold treatment and bring the patient back in 2 months. If OCT shows the macula is still dry at that visit, I have the patient return the following month to receive another injection.

Alternatively, if fluid has reaccumulated 2 months after a dry OCT, my patients receive ranibizumab at that visit. In other words, all of my patients get a minimum of 4 ranibizumab doses per year.

Is there solid science behind this approach? Probably not, but an aspect of the PrONTO[1] trial that bothers me is that a certain amount of fluid was allowed to accumulate before retreatment. (See "The PrONTO Study.") I like the idea of having a consistently dry macula. It is based on theory alone at this point, but perhaps the delicate photoreceptors sustain damage every time the macula thins and thickens. It might be possible to achieve a better outcome if we keep the macula dry over the course of treatment.

Dr. Apte: We all want to reduce the number of injections for the sake of our patients and our practices. However, I do not hesitate to continue treatment when it appears the disease in a particular patient is aggressive. In those cases, following the MARINA and ANCHOR protocol of monthly dosing may be the most appropriate decision.

Dr. Rosenfeld: So you sometimes use monthly dosing?

Dr. Apte: Yes, in cases where I have not seen evidence of a dry macula or if a switch to off-label bevacizumab (Avastin, Genentech) has been unsuccessful, I would consider continued monthly dosing. I also might dose monthly in a situation where OCT and the fluorescein angiogram (FA) showed the disease had stabilized but then recurred. That tells me the lesion is more aggressive and makes me more inclined to continue treatment. I follow a patient like that more closely, and I am not hesitant to give additional injections as needed.

The PrONTO Study

PrONTO[1] is a Phase 1/2, 2-year, single-center, uncontrolled, open-label study (n=40) evaluating variable dosing with 0.5-mg of ranibizumab (Lucentis, Genentech) guided by optical coherence tomography (OCT). Patients receive a 0.5-mg intravitreal injection of ranibizumab at baseline and months 1 and 2. Thereafter, they receive additional injections if any of the following criteria are met since last visit:

- Visual acuity loss of ≥5 letters with any fluid on OCT
- Increase in central retinal thickness ≥100 µm
- New hemorrhage
- New classic choroidal neovascularization (CNV)
- Persistent fluid detected by OCT 1 month after an injection.

The visual acuity results achieved at 1 year in the PrONTO study were comparable to the results achieved with monthly dosing in the Phase 3 MARINA and ANCHOR trials ranibizumab.

Reference:

1. 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;143:566-583.

KEEPING THE MACULA FREE OF FLUID

Dr. Rosenfeld: I think everyone agrees that we want to keep the macula dry. The PrONTO study was designed to demonstrate that if a small amount of fluid accumulates, more fluid follows, so our conclusion was that treatments should try to maintain a dry macula, but our data suggest that a small amount of fluid was not detrimental. This should be reassuring to both patients and doctors if a monthly return isn't possible because of scheduling conflicts, and the patient has to delay a return visit to the office. At least we know it's OK to have a small amount of fluid in the macula for a short time, and it's not an emergency even if the fluid returns.

The conclusion of the PrONTO study wasn't that we should purposely allow fluid to accumulate.[1] The goal was to get the macula dry but minimize the number of injections. In fact, in the second year of the PrONTO study, we amended the protocol to allow retreatment when there was any qualitative change on OCT no matter how miniscule the fluid change. We did not inject even when the macula was dry as in the "treat and extend" strategy, because we wanted to know the length of the fluid-free interval so we could inject as infrequently as possible. Now we know the two extremes: Monthly injections vs. PrONTO-style injections known as "treat and observe."

What is your strategy for keeping the macula dry? One strategy is monthly dosing, another is treat and observe, and the third intermediate strategy is known as treat and extend.

Dr. Brown: For patients with good initial visual acuity or in whom we are dealing with the primary eye, I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks. If fluid is absent at that visit, I give another injection and see them in 10 weeks.

Dr. Rosenfeld: You always administer 3 initial monthly doses?

Dr. Brown: Yes, I administer 3 doses in all cases except extrafoveal lesions.

Dr. Rosenfeld: Who else on the panel always administers 3 doses?

Dr. Apte: I do.

Dr. Reichel: I do not. I am a big believer in prn dosing. I give patients 1 injection and see them 4 weeks later. If the macula is dry, I see them in another 4 weeks.

Dr. Hariprasad: I do not necessarily give 3 initial doses. I give as many consecutive monthly doses as necessary to dry the macula.

Dr. Brown: Even though I am giving every patient 3 initial monthly injections, I look at the macula at each of those visits. If the macula is dry at 1 month, I think we have a good chance of maintaining a dry macula after 3 injections. If the macula does not leak, hallelujah! Every time it does leak, I go to the treat-and-extend strategy.

Dr. Rosenfeld: So, you do not waste a visit. If a patient comes in, you treat whether the macula is dry or wet?

It may be that the fewer injections we give, the more likely we are to maximize vision. Even if a small amount of fluid appears, we may lose the battle but win the war by giving fewer treatments.

— Elias Reichel, MD

Dr. Brown: Yes, but if the macula is dry, I extend the visit interval. If the macula is wet, I bring the patient back much sooner. Treating and extending reduces the number of times the macula accumulates fluid. Any time fluid appears, we have the chance of degradation. Any time we have to dry the macula again, we have another chance for a retinal pigment epithelium (RPE) tear.

Dr. Reichel: I see patients 4 weeks after the initial injection. If the macula is still wet at that time, I give another injection and see them in 4 weeks. If the macul is dry after 2 cycles, I may extend the visit interval to 6 weeks. In general, I am seeing each patient every 4 to 6 weeks. It is a lot of visits, but it ends up being a reduced number of injections overall.

What makes me uncomfortable about treating and extending is that I cannot predict whether fluid will accumulate during that interval. I have seen some patients from the ANCHOR and MARINA trials do really well but then accumulate fluid at an unpredictable time. I do not want to miss that.

Dr. Rosenfeld: As we stated previously, no one wants to see fluid in the macula. However, one point that the PrONTO study demonstrated is that the macula, once dry, can tolerate some reaccumulation of fluid; however, this happens gradually and does not come rushing back like we have seen following photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics).

Dr. Reichel: We may learn in the future that monthly injections necessitate monthly injections because we are upregulating VEGF each time we treat. It may be that the fewer injections we give, the more likely we are to maximize vision. Even if a small amount of fluid appears, we may lose the battle but win the war by giving fewer treatments.

Dr. Apte: After 3 initial monthly injections, I follow a treat-and-observe approach. Even when the macula is dry after 3 injections, I see the patient in 4 to 6 weeks. That way, I do not miss the patients who leak in the interim. But

Based on the clinical data, I believe we need an initial quenching of VEGF. Yes, there is a theoretical positive feedback loop with anti-VEGF treatment, but that is still experimental. I am not willing to treat only once and follow a prn regimen until I am convinced there is clearly a mechanism that supports that type of regimen. It is important to note that only the monthly dosing scheme has been proven for ranibizumab and all others are experimental and still need to be proven in a large-scale clinical trial.

Dr. Rosenfeld: Whether we use a treat-and-observe or treat-and-extend paradigm, we will find that most patients fall into a pattern of retreatment every 6 to 12 weeks. However, there will be some patients who really fall outside this pattern and need very few retreatments.

Throughout 2 years of treating and observing, this group of patients might receive 3 treatments while the treat-and-extend approach might result in 10 treatments if the patient gets 3 initial monthly injections followed by an injection every 3 months whether needed or not. That's OK as long as we realize that some patients might receive injections that aren't necessary, but they aren't harmful either, just costly with a very small risk of endophthalmitis.

It is reassuring to know that even with monthly dosing over 2 years in the MARINA and ANCHOR trials, a downward trend in visual acuity was not observed. It is unlikely that chronic treatment is deleterious to the macula, and endophthalmitis was very rare in the studies. Perhaps we will find that is not the case after 3 or 4 years, but it is unlikely that treating more often than is absolutely necessary is deleterious.

Dr. Reichel: It may not be harmful, but we may be increasing the risk of endophthalmitis and the economic burden by treating more often than is absolutely necessary.

Dr. Rosenfeld: I let the patients decide whether I will use the treat-and-observe or the treat-and-extend strategy. Some do not want an injection unless they absolutely need it. Others say the last thing they want to do is come back again the next month and wait.

Dr. Hariprasad: I have seen that divergence in my patients, too. That is why I let them decide.

RELATIVE IMPORTANCE OF RPE TEAR RISK

Dr. Rosenfeld: Would anyone on the panel not treat a neovascular AMD patient with an intravitreal anti-VEGF agent because of the risk of an RPE tear?

Dr. Apte: Whether a patient is at risk for an RPE tear is not a consideration for me in terms of whether I would use an anti-VEGF agent.

Dr. Rosenfeld: Other than a serous pigment epithelial detachment (PED), is there anything that makes you concerned that a patient might develop an RPE tear?

Dr. Reichel: A retinal angiomatous proliferative (RAP) lesion. Also, an RPE tear is not necessarily the end of the world. If it rips through the fovea and vision declines, of course, that is a serious problem. But if vision remains good after the tear, often those eyes can maintain good vision for a long time. Often, the tear does not continue once it stabilizes after the initial insult.

PERI-INJECTION ANTIBIOTICS

Philip J. Rosenfeld, MD, PhD: How do you prep patients for an intravitreal injection of an anti-vascular endothelial growth factor agent?
Rajendra S. Apte, MD, PhD: For the most part, I follow the consensus panel guidelines that were published in *Retina* in 2004.[1] I use povidone iodine, gloves and an eyelid speculum. I use a topical, but not subconjunctival, anesthetic.
Prior to the injection, I use a broad-spectrum topical antibiotic. I also displace the conjunctiva because I would rather have the egressed vitreous under the conjunctiva than coming out of the eye in order to reduce the theoretical risk of an infection. I follow the injection with povidone iodine and a topical antibiotic. I do not check IOP after the injection. I use an indirect ophthalmoscope to make sure the optic nerve head is perfused.
Dr. Rosenfeld: Does the rest of the panel also use antibiotics before the injection?
David M. Brown, MD: In most cases, we prescribe topical antibiotics for 3 days prior to the injection.
Elias Reichel, MD: I do not use preinjection antibiotics.
Seenu M. Hariprasad, MD: I use a fourth-generation fluoroquinolone for 30 minutes (1 drop every 10 minutes) before the injection and also afterward for 3 days qid.
Dr. Rosenfeld: I do not use antibiotics prior to injection.
Whether it is necessary to use antibiotics after the injection is a controversial issue. Currently, at least one of the Diabetic Retinopathy Clinical Research Network's ongoing studies is leaving the use of antibiotics after intravitreal injections to the discretion of the treating physician. For me, it is difficult to imagine that anything we apply topically will matter if bacteria are introduced into the vitreal cavity, but we do not know for sure.
Dr. Hariprasad: There is evidence in the literature that fluoroquinolones applied topically can decrease conjunctival bacterial load greater than betadine alone. Obviously, we don't know for certain that peri-injection antibiotics actually change the rate of endophthalmitis. However, given the severe consequences of endophthalmitis, it makes sense to me to decrease conjunctival bacterial load to the best of my ability before passing a needle through the conjunctiva into the vitreous cavity.

REFERENCE

1. Aiello LP, Brucker AJ, Chang S, et al. Evolving guidelines for intravitreous injections. *Retina*. 2004;24:S3–S19.

Dr. Apte: Unfortunately, all of the RPE tears that have occurred in my patients have involved the fovea.

Dr. Rosenfeld: Does everyone agree that even though anti-VEGF therapy may accelerate a small percentage of eyes toward an RPE tear, we do not have an option other than to treat these patients?

Dr. Reichel: Certainly, the effect of the anti-VEGF agent shrinking the neovascular membrane causes more tears than leaving it alone. However, if we want to achieve better vision, we have to use the treatment.

DEFINING AN ANTI-VEGF THERAPY FAILURE

Dr. Rosenfeld: With anti-VEGF therapy, what do you consider a treatment failure?

Dr. Brown: A treatment failure is when multiple anti-VEGF treatments have been applied, and fluid and perfusion persist on OCT and FA.

Dr. Reichel: It is unclear what is happening in eyes where a thin layer of subretinal fluid persists while vision remains as good as 20/40 or 20/50. I am not sure whether that is a treatment success or a treatment failure. To me, a failure is when I am treating a patient and either subretinal fluid is increasing or vision is declining for no

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