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Treatment Paradigms in AMD Management: Assessing Consistent Long-Term Dosing

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EXHIBIT
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CONTENT SOURCE

This continuing medical education (CME) activity captures content from roundtable discussion held in June of 2017.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Understand the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF therapies for common retinal diseases, including AMD.
- Discuss the ocular and systemic effects of anti-VEGF therapies and how to educate patients on appropriate expectations.
- Develop plans to initiate treatment for conditions such as AMD using anti-VEGF agents, as well as better understand when to change therapeutic strategies.

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Treatment Paradigms in AMD Management: Assessing Consistent Long-Term Dosing

Age-related macular degeneration (AMD) is a chronic, progressive disease. It is a leading cause of blindness in developed countries,[1-4] with an overall global prevalence of 8.69%. AMD is most prevalent in patients older than 60 years, with incidence rates expected to increase as the population ages—approximately 228 million people will be diagnosed with AMD in 2040.[5] There is no cure, but in today's world, AMD can be managed through medical intervention via intravitreal anti-VEGF injections in a fixed, pro re nata (PRN) or treat-and-extend dosing regimen. This roundtable gathered retina specialist experts to discuss the pros and cons of these treatment options and the data supporting them, long-term outcomes and vision loss with current treatment options, and the clinical pearls we can learn from pivotal studies. It also tackles the cause and treatment of geographic atrophy.

– W. Lloyd Clark, MD, moderator

COMPARING AMD TREATMENT REGIMENS VS REAL-WORLD OUTCOMES

W. Lloyd Clark, MD: When examining the long-term treatment strategies, outcomes, and expectations of anti-VEGF therapy for AMD, three dosing strategies surface: gold standard monthly treatments, PRN, and treat-and-extend. The seminal papers supporting monthly AMD anti-VEGF therapy — MARINA, ANCHOR, and VIEW 1/VIEW 2[6-10] — provided us with pivotal information regarding the clinical viability of monthly treatment. What are the positive and negatives to monthly therapy, and what data support this regimen?

David Brown, MD, FACS: Everyone agrees the best treatment available is monthly therapy if the patient has the time to devote to it. The data is strong. ANCHOR and MARINA both examined ranibizumab as a monthly treatment; for the first time, patients with wet AMD were able to show visual improvement. In ANCHOR (n = 423), patients were randomized to monthly ranibizumab at 0.3 mg or 0.5 mg plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy.[8] Primary endpoint was loss of fewer than -15 letters from baseline visual acuity (VA) at 1 year.

The results were staggering. A total of 35.7% of patients treated with ranibizumab 0.3 mg and 40.3% of patients treated with ranibizumab 0.5 mg showed VA gains of +15 letters or more.[8] In contrast, patients treated with active verteporfin therapy actually lost an average of -9.5 letters during the same timeframe.

MARINA randomized patients (n = 716) to monthly ranibizumab intravitreal injections (either 0.3 mg or 0.5 mg) or sham injections.[6] Like ANCHOR, the primary endpoint was loss of fewer than -15 letters from baseline at 1 year. The results from MARINA were similar to ANCHOR: VA improved by +15 or more letters in 24.8% of patients in the 0.3 mg ranibizumab group and in 33.8% of patients in the 0.5 mg ranibizumab group, compared with 5% of patients of the sham-injection group.[6]

Monthly therapy is also safe; patients will not experience recurrent fluid or recurrent hemorrhage.

So why do we do anything else, but monthly anti-VEGF injections for AMD patients? Unfortunately, the real world gets in the way, and patients miss appointments. The average patient gets sick, breaks a hip, and cannot have a family member take off work every month to bring them to our clinics.

Now, VIEW 1 and VIEW 2 illustrated that we can extend that monthly treatment to every 2 months with aflibercept with similar results as monthly ranibizumab therapy. These parallel studies randomized patients to intravitreal aflibercept at 0.5 mg monthly, 2 mg monthly, or 2 mg every 2 months after three initial monthly doses or ranibizumab 0.5 mg monthly.[10] All aflibercept groups were noninferior and, on average, clinically equivalent to monthly ranibizumab, demonstrating that an every 2-month regimen with aflibercept is an effective treatment strategy for most patients with wet AMD.

The problem is patients want the least amount of treatments possible, and every 2 months is still too frequent for many patients. That is why in my practice, and I think most of the country, we use treat-and-extend. We treat until dry, we extend until the patient has evidence of active exudation, and then we back off and treat at an interval that avoids recurrent leakage.

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The TREX-AMD trial validated this as a treatment approach by comparing treat-and-extend to monthly ranibizumab.[11] Treat-and-extend is not quite as effective as monthly anti-VEGF therapy, but it was very close with minimal exposure to risk. At 24 months, patients in the monthly ranibizumab group gained +10.5 letters, while patients in the treat-and-extend cohort gained +8.7 letters.[11] No patient on ranibizumab lost more than -2 letters, but five treat-and-extend patients lost at least -15 letters. We know the treat-and-extend strategy is not perfect, but it is the treatment schedule most patients can comply with, and it is the compromise they are willing to make.

Peter K. Kaiser, MD: There is no question fixed monthly or every other month in the case of aflibercept injections is the gold standard and offers the best visual outcomes. We have seen this in numerous head-to-head studies, including CATT, IVAN, and SUSTAIN.[12-15] This treatment regimen, however, is not sustainable.

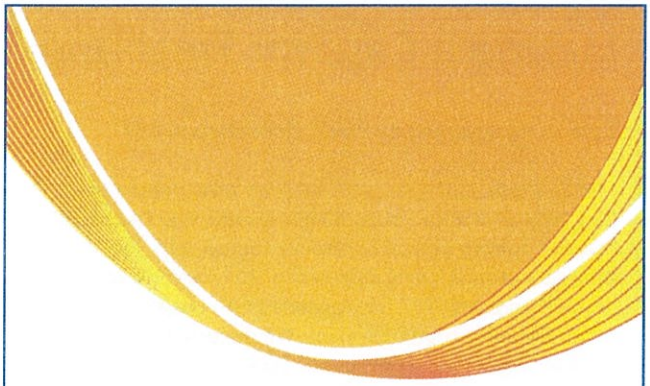
CATT was a randomized clinical study (n = 1,185) that set out to answer two questions: are bevacizumab and ranibizumab clinically equivalent, and does PRN dosing yield the same visual outcomes as monthly injections? In the 1,107 patients who were followed during year 2, ranibizumab and bevacizumab had similar VA gains over a 2-year period, with both drugs resulting in a mean +0.5 line gain compared to PRN. More patients in the PRN groups lost more than -3 lines of vision and had persistent retinal fluid than those in the monthly groups. Plus, switching from monthly to PRN resulted in a greater mean decrease in vision during year 2 (-2.2 letters).[12]

IVAN (n = 610), a study from the United Kingdom, also compared bevacizumab and ranibizumab on a monthly or PRN dosing schedule. At 1 year, the comparison of VA between bevacizumab and ranibizumab was inconclusive because bevacizumab did not meet the prespecified noninferiority criteria of -3.5 letters. Continuous monthly treatment, however, led to smaller choroidal neovascular (CNV) lesions, less fluorescein leakage, and less fluid on the OCT.[13]

SUSTAIN (n = 513) examined ranibizumab only, comparing the safety and efficacy of monthly injections to a PRN dosing in treatment-naive patients. Patients were given three initial monthly injections of ranibizumab 0.5 mg and evaluated monthly. Patients were retreated if more than -5 letters were lost.[14]

The results were not too surprising given the other data. Safety was comparable to the favorable tolerability profile of ranibizumab illustrated in previous studies. VA was at the highest point after the first three monthly injections, decreased slightly under PRN during the next 2 to 3 months, and was then sustained throughout the treatment period.[14]

What we should be taking from all these studies is that it does not really matter what anti-VEGF drug you are using in terms of safety and efficacy. What matters is the dosing schedule. Fixed monthly dosing always performed better. The problem is that monthly anti-VEGF therapy is an unsustainable treatment regimen, especially as we get further and further out from baseline. To me, PRN is not an option; it essentially equates to extend and neglect.



"To me, PRN is not an option; it essentially equates to extend and neglect."

—Peter K. Kaiser, MD

In my opinion, the next best thing is a treat-and-extend regimen.

LUCAS showed that treat-and-extend can have good visual outcomes.[16] This study randomized 441 patients to either bevacizumab 1.25 mg or ranibizumab 0.5 mg on a treat-and-extend protocol. Injections were given every 4 weeks until the patient became dry. The treatment then was extended by 2-week intervals for a maximum of 12 weeks until recurrence. After recurrence, the treatment interval was shortened by 2 weeks at a time. Bevacizumab was equivalent to ranibizumab, with +7.4 and +6.6 letters gained, respectively.

A treat-and-extend treatment regimen offers us the ability to be proactive with our treatment and avoid the recurrences that you wait for with a PRN regimen. So, to me, treat-and-extend is the best treatment for wet AMD, given the compliance issues with monthly injections.

David Eichenbaum, MD: According to the 2016 Preferences and Trends Survey from the American Society of Retina Specialists, about 70% of all US retina specialists default to treat-and-extend for wet AMD, and only 5% recommend monthly treatment.[17] It is not difficult to see why. When I am treating new patients and discussing anti-angiogenic injections with them, the first thing question patients ask is, "How many of these do I need?," followed by, "When do I have to come back?" What patients immediately think about is less frequent injections. They want fewer visits. Their family wants them to come in less. That is what we are up against as clinicians.

When I explain to the patient that I will attempt to give them fewer injections over time, I am alluding to treat-and-extend, even though I know the data is not as strong as monthly treatment. Like Dr. Brown, I treat until dry, then I slowly extend until the eye tells me it cannot extend any further. I will then pull back and generally leave that interval in place for a long time.

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