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

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CONTENT SOURCE

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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 2⁶⁻¹⁰ — 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.

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.

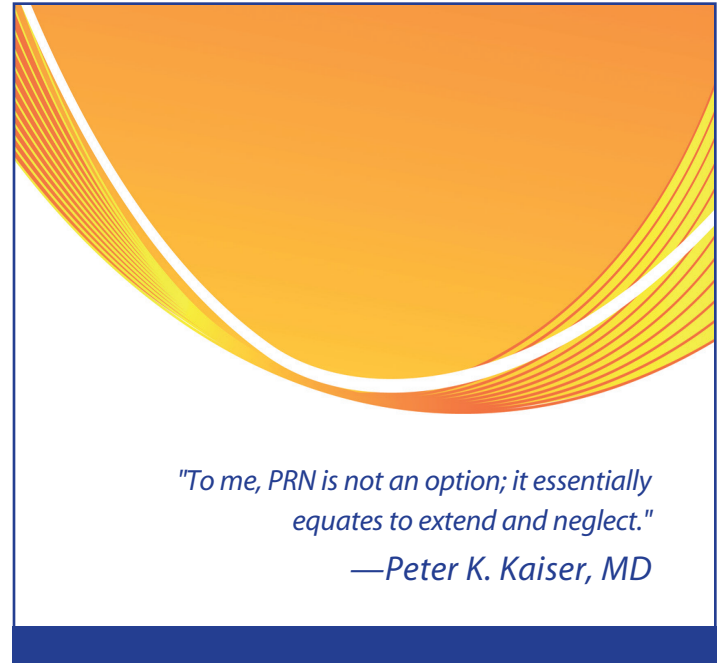
CATT was a randomized clinical study (n = 1,185) that set out to answer two questions: are bevacizumab and ranibizumab clinically equivalent, and does PRN dosing yield the same visual outcomes as monthly injections? In the 1,107 patients who were followed during year 2, ranibizumab and bevacizumab had 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-naïve 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.



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.

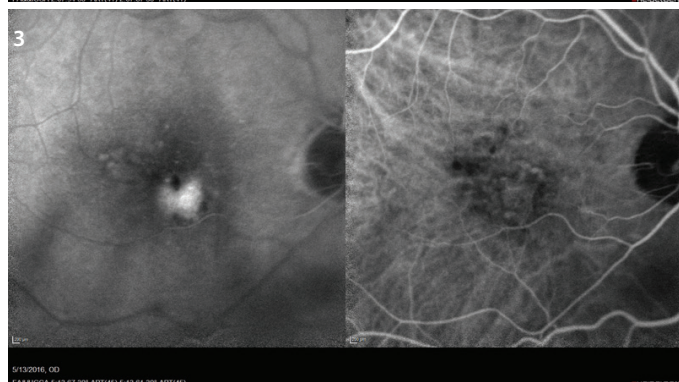
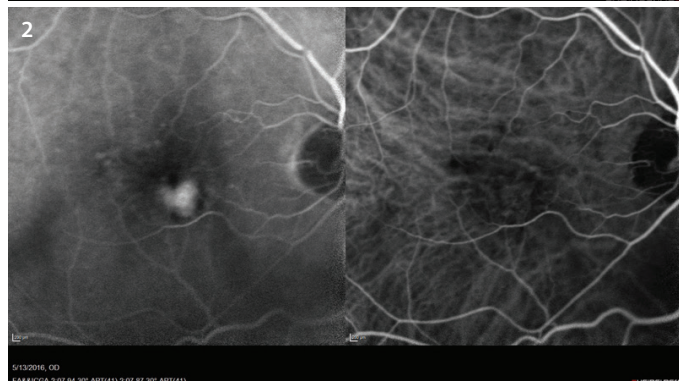
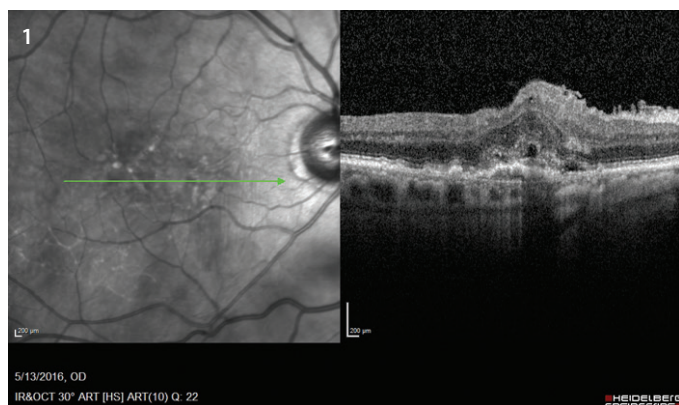
David Eichenbaum, MD: According to the 2016 Preferences and Trends Survey from the American Society of Retina Specialists, about 70% of all US retina specialists default to treat-and-extend for wet AMD, and only 5% recommend monthly treatment.¹⁷ It is not difficult to see why. When I am treating new 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.

Making a Case for Treat-and-Extend

Case study supplied by David Eichenbaum, MD

In this case, a 77-year-old Caucasian male presented in May 2016 with vision of 20/63 in the right eye. The initial spectral-domain optical coherence tomography (OCT) scan showed a central foveal thickness of 361 microns. Based on his OCT and early/late indocyanine green images (Figures 1-3), I recommended treatment. We discussed commercially available agents for treatment of neovascular macular degeneration and the patient requested aflibercept. We



Figures 1-3. Patient's vision is 20/63 with a central foveal thickness of 361 microns in May 2016.

began monthly injections of aflibercept, and he continues on aflibercept throughout this case report. In November 2016, he returned following extension to 6 weeks from the last aflibercept injection. At the time, his vision was 20/50+2, and on OCT the central foveal thickness had reduced substantially to 294 microns (Figure 4). I, again, gave a treatment and recommended a 6-week interval, and I then continued extending by one week at each subsequent visit. At his last visit in August 2017, he was 8 weeks post-injection. His vision was 20/40+2, and OCT showed a central foveal thickness of 309 microns, but with re-accumulation of subretinal fluid adjacent to the shallow PED (Figure 5). Despite the improvement in vision, the recurrence of subretinal fluid and increase in foveal thickness are consistent with recurrent choroidal neovascular activity, and I contracted the treatment interval to 7 weeks. If the vision is maintained, and the fluid regresses, I plan to continue the patient at a 7-week interval. If the fluid persists or accumulates further, I plan to reduce the treatment interval again to 6 weeks.

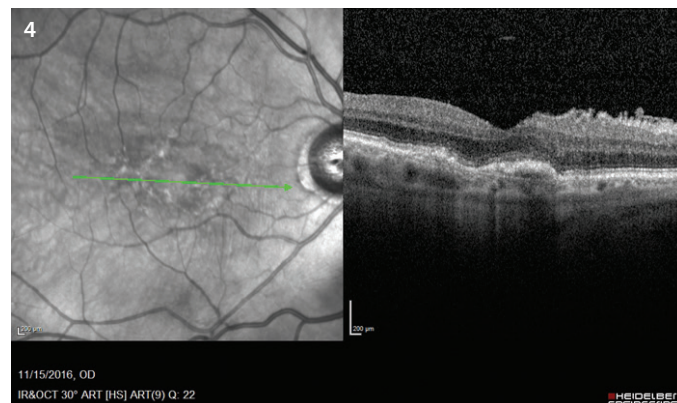


Figure 4. Patient's vision is 20/50+2 with a central foveal thickness of 294 microns in November 2016.

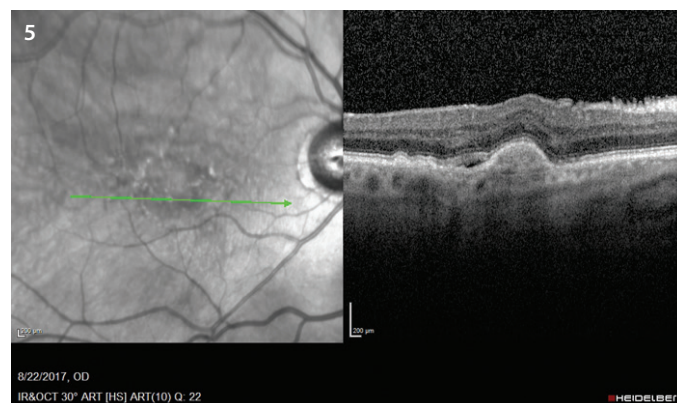


Figure 5. Patient's vision is 20/40+2 with a central foveal thickness of 309 microns in August 2017.

Dr. Clark: Is there a role for PRN therapy today? Is there a clinical scenario where it still makes sense and can be provided effectively?

Dr. Brown: In about 10% of my patients, three injections will shut down their choroidal neovascularization (CNV), and they do not need another one. If a patient totally dries out with three shots, I am willing to move to PRN. I am waiting for the patient to recur. If a patient gets to 10 weeks without recurrence, he or she is one of the lucky 10%. But the fact is, 90% of my patients recur at 6, 8, or 10 weeks, and then move to treat-and-extend for the rest of their life. Treat-and-extend does not mean testing an upper treat-and-extend interval forever. It is about finding the fixed-dose regimen that controls their disease; 90% of patients live with that interval and preserve their vision. The other 10% continually negotiate to extend their treat-and-extend interval. I tell these patients they can negotiate with their disease, but they will lose vision.

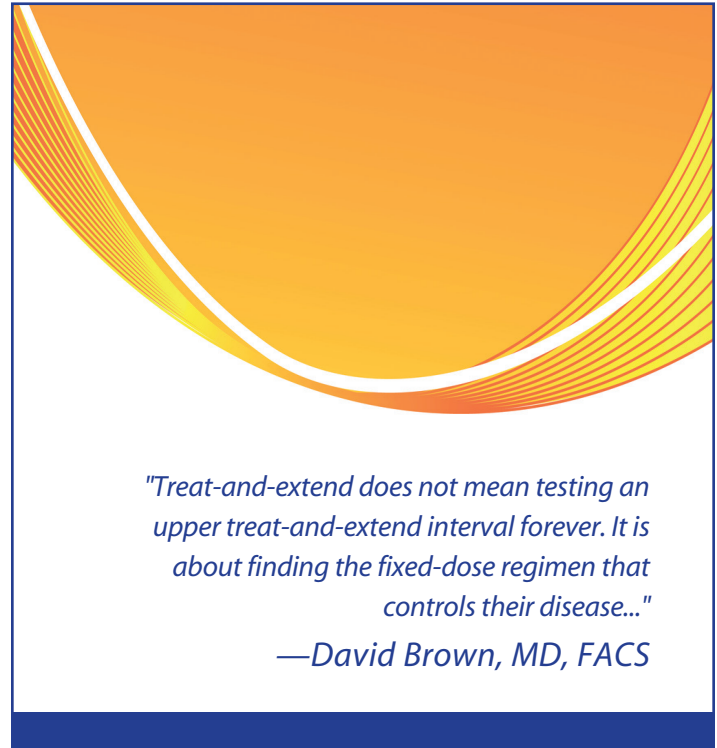
Dr. Kaiser: I think PRN is useful in patients who need a limited number of injections, such as vasculopaths who may have had a stroke or in patients who have macular atrophy encroaching on the center of the fovea. In these situations, I try to limit the number of injections. One could argue that you are limiting the number of injections in the later years when using treat-and-extend, but I try to limit the injections even further in these patients.

Dr. Clark: Many of our colleagues in community practice still use PRN today. I do not because I find that PRN therapy typically leads to undertreatment and to increased disease activity for a long period of time. That is one of the main drivers of long-term vision loss in AMD.

Dr. Kaiser: Part of the problem is that when people talk about PRN, they are not talking about the PRN regimen tested in clinical studies. PRN did well in studies because patients were seen monthly. In real life, they are being seen on increasingly longer intervals between PRN visits, which may result in a significant bleed or leakage that cannot be corrected with additional injections. Thus, if you are going to use PRN, you truly need to see the patient monthly.

Dr. Eichenbaum: I agree—you do have to see the patient monthly for years to achieve the good results seen in clinical trials with true PRN therapy. If you do not see the patient monthly, you wind up with progressive retinal neglect. There is also the “PRN-and-extend” concept, which is really rooted in no randomized controlled trial evidence. You wind up with very few injections, and you probably get results similar to SAILOR,¹⁸ which are pretty dismal.

SAILOR included two cohorts totaling 4,300 patients. Patients in cohort 1 were randomly assigned to ranibizumab 0.3 mg (n = 1,169) or 0.5 mg (n = 1,209) for three monthly loading doses. Dose groups were stratified by AMD treatment history, either treatment-naïve or previously treated. Patients in cohort 1 were retreated on the basis of optical coherence tomography (OCT) or VA criteria.

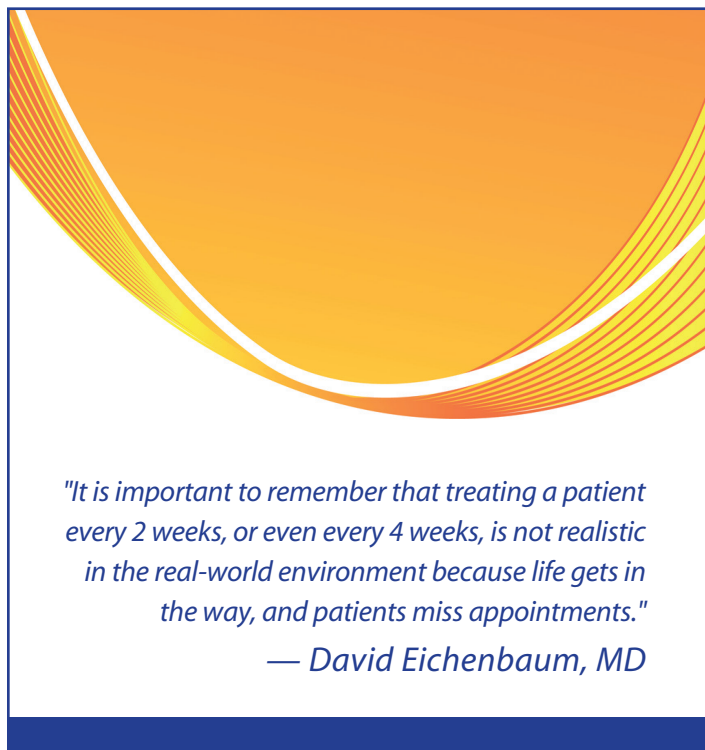


Patients in cohort 2 (n = 1,922) received an initial dose of ranibizumab 0.5 mg and were retreated at physician discretion. The average number of ranibizumab injections was 4.9 for cohort 1 and 3.6 for cohort 2. At 1 year, cohort 1 treatment-naïve patients had gained an average of +0.5 (0.3 mg group) and +2.3 (0.5 mg group) letters. Previously treated patients had gained +1.7 (0.3 mg group) and +2.3 (0.5 mg group) letters.¹⁸

DETERMINING TREAT-AND-EXTEND INTERVALS AND PED TREATMENT

Dr. Clark: How long do you extend treat-and-extend intervals? What are you looking for, and what is your response when you see recurrences?

Dr. Eichenbaum: I individualize the treatment and stick to the available data as best as I can. I am a 2-week extender, which is in line with treat-and-extend studies such as LUCAS.¹⁶ A difference in my recommended extension intervals is that I will often extend a patient from maybe 4 weeks to 6 weeks, but then leave the patient at 6 weeks for a few cycles before the next extension. I am concerned about disease activity when I see subretinal fluid on the OCT or subretinal hemorrhage on a dilated funduscopy exam. I will return to the interval when that fluid was dry or to the interval at which there was no hemorrhage. For example, if a patient went from 6 weeks to 8 weeks, and there is fluid at 8 weeks, I will pull them back to 6 or 7 weeks, shoot another scan, and leave them there for at least three or four cycles. After several months, we can discuss extension again, at which point I would try 7 to 8 weeks. Often, the patients are pushing for more extension throughout this process.



Dr. Clark: That sounds a lot like the TREX-AMD study.¹¹ Does anyone else do this?

Dr. Brown: Usually, but with the exception of new subretinal pigment epithelium (sub-RPE) fluid. That indicates a leakage from new CNV activity, which needs a more aggressive treatment approach. I use the same treatment strategy for new sub-RPE fluid as was used in the CATT trials,¹² but I do not chase it if it does not go away. If a fibrovascular pigment epithelial detachment (PED) pops up with an increased dosing extension, however, I have found it will respond and regress if you treat it more aggressively and tighten the dosing interval.

Dr. Eichenbaum: I am sometimes nervous about completely flattening out subfoveal fibrovascular PEDs because of the de novo atrophy data from HARBOR.¹⁹ Post hoc analysis found that although the presence of PED was a retreatment criteria in HARBOR, patients with complete resolution of PED did not necessarily see an additional vision benefit and were more likely to demonstrate macular atrophy at month 24. Therefore, my primary goal with PEDs is not to purposefully flatten them out because there are reasonable post hoc data that doing so increases the risk of de novo atrophy at the site of that lesion.

Dr. Brown: There is certainly controversy in that. To me, fluid is bad and activity is bad, and I want to get rid of it. I am more in the favor of overtreating than undertreating. There is no convincing evidence on the atrophy scare, and I am not going to undertreat patients based on a hypothesis that has no solid data behind it. We have concrete data that undertreatment leads to vision loss and

blindness. On a population basis, it is like saying that no one in the United States should ever fly in an airplane because Dan Martin read about an airplane crash.

Dr. Eichenbaum: I tend to inject more now than I did when I started practice 10 years ago. I push hard on subretinal fluid and subretinal blood, but I do not push hard specifically on fibrovascular PEDs. I agree that we are probably not causing geographic atrophy (GA) in flat retinas, but I do worry about inciting atrophy by flattening out a big PED.

Dr. Brown: I think a bigger problem with fibrovascular PEDs is letting them fluctuate in size. Think of it like an elastic balloon that is repeatedly inflating and deflating. This action is likely to result in a tear in the balloon. Once the PED is stable, I would rather keep the patient at their interval and not extend further.

Dr. Kaiser: When you have a fibrovascular PED, what concerns me most is seeing the CNV on the undersurface of the RPE on the OCT. By definition, this is a type 1 CNV, but I worry about rapidly flattening the PED if the CNV is right underneath the RPE surface. This can lead to RPE tears. Therefore, I try to be a little less aggressive in terms of rapidity, which is detailed in a paper we wrote in 2010 in *Retina*.^{20,21}

Dr. Clark: How do you measure PED height in your clinical practice? Do you measure them manually or is this more of a subjective gestalt?

Dr. Eichenbaum: I do not measure them manually. It is more of a gestalt for me.

Dr. Kaiser: I do not think the average retina specialist needs to measure PED height. In HARBOR, we were very precise at our reading center about how the PEDs were measured,¹⁹ but I think in clinical practice really what you are trying to see is change over time, not precise measurements. What is important is the ability to look at the PED sequentially over time to make sure that it is decreasing in size. If the PED is enlarging or a new PED is forming, I consider that fluid just like I would any fluid above the RPE. But, I do not think you have to take out the calipers and measure it.

LONG-TERM TREATMENT FACTORS IMPACTING VISION LOSS

Dr. Clark: With long-term data from the CATT trial, we now see data emerging that demonstrates loss of the vision gains out to 4, 5, and 6 years.¹⁵ Similar findings have been seen in other loosely-structured, longer term follow-up protocols, such as SAILOR and SEVEN-UP.²² One-third of patients in SEVEN-UP had visual declines of -15 letters or more 7 years post-ranibizumab therapy in the ANCHOR or MARINA trials. In particular, CATT illustrated three main causes of this: recurrent disease activity, geographic atrophy, and sub-retinal fibrosis. Is this a big problem in your practice?

Utility of Fluorescein and OCT Angiography in Real-World Practice

Dr. Clark: We use fluorescein angiography (FA) to identify CNV membranes, but can it be used to predict outcomes or how patients will respond to treatment?

Dr. Eichenbaum: I use liquid angiography less than I used to. I do get a traditional FA on all new wet AMD patients. I think that the angiographic findings have some predictive value for injection burden, anatomic response, and visual response. I do not talk to individual patients about my predictions for their lesions based on the angiographic findings because they are variable; each patient responds differently. A true type-2, well-defined classic lesion that is clear on angiography, however, is likely to respond faster and require less overall burden of care than a large, poorly defined, predominantly occult lesion. Obviously there is no hard-and-fast rule, and I do not think we can depend on the pre-treatment angiogram to give us a sensitive and specific predictor of response. But, it can inform our own “internal monologue” in each case.

Dr. Clark: How are you using OCT angiography for diagnosis and for any predictors of a treatment response?

Dr. Kaiser: We have not learned enough from OCT angiography to determine the imaging biomarkers that would allow us to make outcome predictions. It is too new. Similar to Dr. Eichenbaum, I still get an FA at baseline. I think it is an important tool in predicting how often a patient will need treatment, and there is some predictive value in knowing if it is a type 1, 2, or 3 lesion. As OCT angiography improves, however, we will use fluorescein angiography less and less in the future.

Dr. Clark: Would anyone repeat the angiogram after baseline?

Dr. Kaiser: It is rare for me to repeat the angiogram after baseline. I may consider repeating it in a nonresponder or a patient who isn't responding like I expected. Usually at that point, however, an ICG angiogram would give me more information than a fluorescein angiogram.

Dr. Brown: I think there is a selection bias of patients who go into trials. Many patients who go into trials are underinsured and enroll because they can get better care in the trial than they can with their own insurance. They enroll on a trial like CATT or VIEW 1 or VIEW 2, which gives them monthly therapy for the duration

of the study, and the patient does very well. But, when the trial is over, the patient goes back to being underinsured and undertreated and they regress.

CATT was a 2-year study funded by the National Eye Institute (NEI). If we are going to get a view of real-world outcomes long term, NEI needs to fund a trial for 5 to 7 years and see how patients do compared to these other studies that were only funded for 2 years. Many of my patients with good insurance who stay outside of trials do well. We all have patients who have great outcomes 10, 12, and 14 years out.

Dr. Eichenbaum: I think there is some truth to what Dr. Brown is saying. If patients have ongoing injections without the burdens of real life, such as cost and time, they do pretty well. These studies prove that. These studies also argue against progressive, injection-related retinal atrophy as a cause of vision loss because the patients do well with more injections and poorer with fewer injections.

Dr. Clark: CATT data showed that 80% of the eyes had recurrent fluid at 5 years.¹⁵ Do you think that is a historical number, and we are doing a better job at managing recurrent fluid today?

Dr. Brown: I do not think the 5-year CATT data are a very convincing. The problem is you do not know what treatment patients received after they left the CATT trial. The data may be a statement that shows that people do not receive the same quality of health care depending on their income level. I think it would be helpful if the NEI would do a long-term, 7-year trial to evaluate how patients do with monthly therapy versus treat-and-extend.

Dr. Kaiser: The results of the CATT 5-year data, as poor as they are, were a wake-up call that we need to be more aggressive in our treatment of wet AMD. Hopefully that will be one of the positive outcomes of the long-term CATT study.

Dr. Clark: Just like the SEVEN-UP and PIER trials,^{22,23} it is a reminder that patients do not do well when fewer injections are given.

In SEVEN-UP, which assessed the long-term outcomes of patients enrolled on ANCHOR, MARINA, and HORIZON, 37% of study eyes on ANCHOR or MARINA had BCVA of 20/200 or worse. Thirty-four percent of ANCHOR and MARINA patients had VA loss of -15 letters or more, with overall a mean decline of -8.6 letters.²²

Patients enrolled on PIER did well initially after the first monthly loading doses, but slowly regressed overtime back to baseline after they were switched to quarterly dosing.²³ Patients lost an average of -3.5 letters 10 months after crossover to quarterly dosing. All these data solidify the idea that we cannot decrease the number of injections. We must stay aggressive in our treatment.

Dr. Clark: Data emerging from the Fight Retina Blindness Study Group from Australia,²⁴ as well as the VIEW 1 extension study and the RANGE trial in the United States, show what maintenance of

long-term vision gains look like in patients with AMD.^{10,25,26} RANGE shows that patients are still maintaining some level of vision gains 5 and 6 years later. There is some deterioration of vision compared to the end of the 2-year active treatment phase. Patients at the end of VIEW 1 gained about +12 letters, on average. For RANGE, patients were still +4.5 letters above baseline 6 years out. Is this a realistic real-world outcome?

Dr. Eichenbaum: I would like to think these are attainable goals. In my practice, I have reliable patients who come in consistently for 5 to 7 years, some for 10 years now, and they tend to do well with ongoing, regular treatment. On average, VA does not remain at year 1 or 2 levels, but as long as I keep treating these patients regularly, they do reasonably well long term. I think that is what we are seeing in the VIEW 1 extension and RANGE trials with more injections in the extension periods than previous trials, such as SEVEN-UP.²²

Dr. Clark: VIEW 1 Extension and RANGE patients received injections every 8 weeks after year 1 for 5 years.^{25,26} Is that treatment realistic in clinical practice?

Dr. Kaiser: VA outcomes should trump hassle. If I tell a patient they need to come in every 2 weeks, the majority would come in every 2 weeks. It comes down to the pact we make with them, and what will they come in for. That said, we have not found a blockbuster treatment for AMD. Anti-VEGF treatments are important, but they are not a game changer in that we have not cured AMD and caused the CNV to disappear. Anti-VEGF injections just get rid of leakage, which is why we have got to keep the treatments going. We are not truly changing the pathology of the CNV. CNV does not regress with our current treatments.

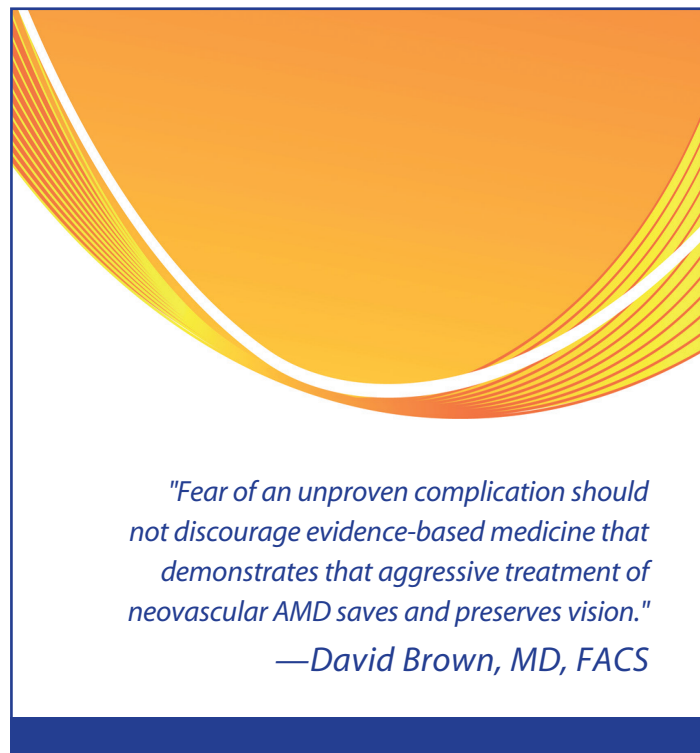
Dr. Clark: Dr. Brown, you were a central participant in the VIEW extension and the RANGE studies. What did you learn from your participation and from the results?

Dr. Brown: There is a big problem with our health care system in that treatment varies widely between insurance plans and their dictates. Some of my patients are treated with bevacizumab and others are treated with aflibercept or ranibizumab.

We also undertreat many of our patients. I firmly believe that we really need a trial to see what happens if we give monthly treatment, or less-than-monthly treatment, for 5 to 7 years. In FIDO,²⁷ however, patients were still averaging a +12.1 letter gain at 7 years after fixed-interval dosing of every 4-8 weeks. Does that treatment strategy provide better outcomes?

Dr. Clark: How often do you think we need to use bevacizumab on our patients to maximize their outcomes?

Dr. Kaiser: Bevacizumab is a great drug. When treating wet AMD, I start all patients on bevacizumab and see how they do, and then switch as needed. There has not been a study that shows any



of the medications to be significantly better like we saw in diabetic macular edema with aflibercept.

Dr. Brown: If I could give bevacizumab every 2 weeks, I could get the same outcomes with it as other drugs. I use bevacizumab more often than I use branded drugs because of its bioavailability, the syringes it comes in, and its molar concentration of anti-VEGF blockade is less.

Dr. Eichenbaum: It is important to remember that treating a patient every 2 weeks, or even every 4 weeks, is not realistic in the real-world environment because life gets in the way, and patients miss appointments. That is why the data from the VIEW 1 extension trial are valuable. They show that if you give patients regular treatment every 8 weeks over the long-term, they do reasonably well.

I do not think we will get those same results with bevacizumab because of its plastic syringes, the processing, the compounding, the bioavailability, and the lack of the controlled and reproducible environment throughout the country. It is less likely to do well with a relatively infrequent injection burden compared to higher-frequency bevacizumab treatment.

It is a balance between relatively frequent treatment using the drugs in our armamentarium and the less frequent treatments that patients desire. The question we are seeking to answer with extension studies using our commercially available agents, as well as our prospective phase 3 registration trials, relates to frequency of treatment and maintaining the VA levels seen with regular, every 4- or 8-week injections.

DEVELOPMENT AND MANAGEMENT OF GEOGRAPHIC ATROPHY

Dr. Clark: What are your strategies for managing patients with geographic atrophy (GA)? Are their clinical characteristics predictive of the future development of GA?

Dr. Brown: Reticular pseudodrusen is a very good marker of people who are going to go to either GA or wet AMD. If we look at our wet AMD and GA populations, 80% have reticular pseudodrusen.²⁸

Dr. Kaiser: I am not sure I believe that macular atrophy is related to long-term anti-VEGF therapy. We should not risk undertreating patients by not giving them anti-VEGF therapy out of fear of developing macular atrophy. If a patient begins to develop atrophy encroaching on the fovea, however, I will try to reduce the number of injections and move the patient from bevacizumab or ranibizumab to aflibercept. In the future, I may move them to RTH258 (brolicizumab) when, and if, that becomes commercially available and extends the interval to 12 weeks.

If the patient develops polypoidal choroidal vasculopathy outside the fovea, I may get an indocyanine green (ICG) angiography and add photodynamic therapy to the treatment regimen. If it is a sub-foveal polyp and macular atrophy is present, I do not add photodynamic therapy to that mix.

Dr. Brown: It is pretty uncommon for me to change therapy if a patient develops GA. GA is a concomitant disease of which we have no specific treatment. We have no data to show that our standard anti-VEGF treatment quickens the development of GA other than a couple of color photography images from CATT at 2 years.¹² I am not going to back off anti-VEGF therapy until data convince me long-term anti-VEGF therapy increases the development of GA.

Dr. Clark: The CATT trial showed that subretinal fibrosis increased the risk of developing GA and that it may be an indicator of long-term results in these patients.^{12,15} With modern anti-VEGF therapy, how significant is subretinal fibrosis in terms of vision loss?

Dr. Eichenbaum: I think that is a historical finding. We do not worry too much about subretinal fibrosis because we do not see as much fibrosis. Patients who develop fibrosis are either undertreated and have recurrences or have relatively chronic lesions at the inception of treatment. They were undertreated in CATT, they entered CATT with chronic lesions, or they had recurrences during the laissez-faire period between 2 and 5 years. Therefore, I do not think subretinal fibrosis is very relevant when treating a new patient who presents promptly.

What I think is more relevant is the issue regarding the development of atrophy in wet AMD patients receiving routine anti-VEGF treatment. Flattening PEDs and creating atrophy corresponding to PEDs is something to think about. I do not

necessarily back off quickly if a PED is flattening, but I do not push harder to flatten the PED, and I will gently extend if there is no subretinal fluid or new subretinal hemorrhage. There is evidence that the presence of a PED probably predicts atrophy in that region if it flattens. That is more relevant to me than worrying that we may be causing diffuse GA by giving regular anti-angiogenic treatment.

Dr. Brown: GA and wet AMD are two different complications of the same disease pathway. Wet AMD is like acute cancer. One has to control the acute disease, as observed in MARINA and ANCHOR, or they will lose the battle early.^{6,8} GA is a totally different ballgame; it is a slow, ongoing disease. I am still going to treat fluid aggressively. Fluid is inherently bad in AMD, and you have to treat it. Fear of an unproven complication should not discourage evidence-based medicine that demonstrates that aggressive treatment of neovascular AMD saves and preserves vision.

NOVEL AGENTS FOR AMD IN THE PIPELINE

Dr. Clark: What drugs are coming down the pipeline that may have better long-term outcomes for patients with AMD?

Dr. Eichenbaum: Preliminary data on brolicizumab, formerly known as RTH258, 3 mg and 6 mg was released recently and showed more than half of patients met the primary endpoint of noninferiority to aflibercept at the 12-week regimen.²⁹ We do not know what that means yet, and analysis is ongoing, but we have a drug coming down the pipeline that could reduce the injection burden on about half the patients.

Dr. Kaiser: I am also very interested to see the results of the brolicizumab studies, HAWK and HARRIER.^{30,31} These studies have enrolled more than 1,800 patients with AMD across 400 centers worldwide. Brolicizumab went head-to-head with on-label aflibercept, and the study results indicate that treatment could be extended to 12-week intervals in at least half of the patients; 57% of patients in HAWK and 52% of patients in HARRIER.²⁹ To me, this offers us the next step—the ability to go even longer between our treatments, but achieve the same visual results. I am excited to see these study results presented in more detail so we can learn how well that drug works.

Dr. Clark: Pegpleranib was an antifibrotic drug for the treatment of AMD that showed much promise but had disappointing clinical results. Safety and efficacy of combination Pegpleranib 1.5 mg and ranibizumab were compared to ranibizumab monotherapy in two phase 3 studies, OPH1002 and OPH1003. Both trials failed to meet their primary endpoints, and did not show additional improvement in BCVA at 12 months with pegpleranib combination therapy compared with standard of care ranibizumab monotherapy.³²

Should we be looking for any more antifibrotic agents down the pipeline?

Dr. Eichenbaum: I hope to see more antifibrotic agents in the future, and companies are looking into antiplatelet derived growth factor treatments. We have not seen the end of it. I am optimistic that we are going to see other drugs that can approach the pathologic processes in AMD for which we currently do not have treatments.

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TREATMENT PARADIGMS IN AMD MANAGEMENT: ASSESSING CONSISTENT LONG-TERM DOSING CME QUESTIONS

1 *AMA PRA Category 1 Credit*™

Expires September 2018

- What is the gold-standard treatment regimen for patients with age-related macular degeneration?**
 - PRN
 - Monthly injections
 - Treat-and-extend
 - Vitamin supplements
- _____ of all U.S. retina specialists default to treat-and-extend for the treatment of wet AMD.**
 - 90%
 - 80%
 - 70%
 - 60%
- According to the panelists, patients with AMD often opt for treat-and-extend over monthly injections because _____.**
 - Monthly injections have unwanted, intolerable side effects.
 - Treat-and-extend has better outcomes over monthly injections.
 - The appointment burden of monthly injections is not realistic.
 - They fear their insurance will not cover the costs.
- The _____ trial showed that treat-and-extend was equivalent to monthly therapy out to 2 years with a reduced treatment burden.**
 - CATT
 - PIER
 - ANCHOR
 - TREX-AMD
- What percentage of patients with geographic atrophy have reticular pseudo-drusen.**
 - 60%
 - 70%
 - 80%
 - 90%
- Agree or disagree: According to the CATT study, geographic atrophy is caused by monthly anti-VEGF injections.**
 - Agree; 5-year CATT data are conclusive.
 - Disagree; 5-year CATT data are inconclusive because the treatment patients received after they left the trial is unknown.
- When treating fibrovascular pigment epithelial defects, you should _____.**
 - Completely flatten them out.
 - Allow them to fluctuate in size ,and observe.
 - Not be concerned if you see choroidal neovascularization on the undersurface of the retinal pigment epithelium.
 - Monitor their height over time and make sure it is decreasing in size.
- According to the panelists, how many weeks should a treat-and-extend protocol be extended by?**
 - 1 week
 - 2 weeks
 - 3 weeks
 - 4 weeks
- The _____ trial(s) illustrated that monthly treatment can be extended to every 2 months with aflibercept with similar results as monthly ranibizumab therapy.**
 - ANCHOR
 - MARINA
 - VIEW 1/VIEW 2
 - LUCAS
- The _____ trial found three primary causes for loss of visual gains long term: recurrent disease activity, geographic atrophy, and subretinal fibrosis.**
 - SEVEN-UP
 - CATT
 - RANGE
 - HAWK

ACTIVITY EVALUATION

Did the program meet the following educational objectives?

Agree Neutral Disagree

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

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Do you feel the information presented will improve/change your patient care? Yes No

Please identify how you will improve/change

Change the management and/or treatment of patients. Please specify: _____

Create/revise protocols, policies, and/or procedures. Please specify: _____

Please identify any barriers to change.

_____ Cost _____ Lack of consensus or professional guidelines _____ Lack of administrative support _____ Lack of experience

_____ Lack of time to assess/counsel patients _____ Lack of opportunity (patients) _____ Reimbursement/insurance issues

_____ Lack of resources (equipment) _____ Patient compliance issues _____ No barriers

_____ Other. Please specify: _____

Satisfaction Measures

The design of the program was effective for the content conveyed in the identified learning objectives Yes No

The content was free of commercial bias Yes No

The content was relative to your practice Yes No

The faculty was effective Yes No

You were satisfied overall with the activity Yes No

Would you recommend this program to your colleagues Yes No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

_____ I certify that I have participated in this entire activity and claim _____ AMA Category 1 Credit(s)™

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