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

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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:

- Discuss the outcomes of pivotal studies in AMD, and how study results may differ from “real-world” dosing methods
- Identify patient subtypes (eg, RAP lesion, pigment epithelial detachments, occult lesions) that will require long-term treatment and imaging evaluation.
- Develop a long-term treatment plan for patients with AMD based on results from clinical trials and extension studies
- Compare the extended safety outcomes of anti-VEGF therapies as published in long-term studies.

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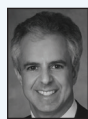
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Treatment Paradigms in AMD Management: Assessing Consistent Long-Term Dosing

Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries,¹⁻⁶ and its prevalence is expected to increase due to the rapidly aging population. With an overall global prevalence of 8.69%, about 228 million people will be diagnosed with AMD in 2040.⁶ Although there is no “cure,” AMD can be managed through medical intervention via intravitreal anti-VEGF in a monthly, pro re nata (PRN), or treat-and-extend dosing (T&E) regimen. This roundtable discusses the unique challenges associated with PRN and T&E, how to translate clinical trial results into real-world practice, and how to maximize disease-free intervals in patients with the neovascular form of AMD. The panel also discusses safety issues such as geographic atrophy and treating patients with known cardiovascular disease.

– W. Lloyd Clark, MD, moderator

PRN AND TREAT AND EXTEND IN CLINICAL TRIALS VS REAL-WORLD APPLICATION

W. Lloyd Clark, MD: Recent pivotal studies in neovascular AMD have supported alternative dosing regimens in patients—PRN and treat and extend—versus our traditional monthly dosing regimen. This discussion will focus on the use of these clinical trials in developing a treatment strategy, how clinical trial treatment regimens differ from those we employ in clinical practice, which tools and strategies in our armamentarium we use to achieve disease-free intervals in patients with AMD, and what our thoughts are on the long-term safety considerations of these treatments.

The CATT trial, which first looked at 2-year and then 5-year outcomes after bevacizumab or ranibizumab for AMD, was pivotal in understanding bevacizumab use relative of FDA-approved therapy.^{7,8} What trials do you use when you consider an alternative dosing treatment strategy in your patients, specifically PRN and T&E?

Carl D. Regillo, MD: Major clinical studies have shown outcomes with PRN dosing are similar to monthly dosing, although not quite as good. The CATT and HARBOR trials provided us with solid data to support that. Five-year CATT data found that 50% of eyes had 20/40 or better visual acuity 5 years post-treatment, confirming that anti-VEGF therapy is a major advance in the treatment of AMD.⁸ HARBOR, which randomly assigned 1,098 patients to ranibizumab 0.5 mg or 2.0 mg intravitreal injections administered monthly or on a PRN basis after three monthly loading doses, had perhaps the best

PRN outcomes out there.⁹ All treatment groups had visual improvement (+8.2 to +10.1 letters) and improved anatomic outcomes, and the PRN groups required approximately four fewer injections.⁹ The problem is, in the real world, we cannot replicate those trial results, so PRN leaves a lot to be desired.

That is certainly a major reason why many of us are moving to the T&E approach. We have long-term data that looks very good. We just looked at the long-term results with aflibercept over 2 years¹⁰ and the visual acuity outcomes are quite comparable to the registration studies.^{11,12} As another example, the 2-year prospective TREX study showed good outcomes with T&E versus the gold standard monthly therapy.^{13,14} The Fight Retina Blindness Study Group from Australia looked at long-term T&E end up to 7 years and showed that visual gains were well-maintained.^{15,16} Maintaining the visual gains beyond 1 and 2 years is key. PRN does not stack up to that.

Rahul N. Khurana, MD: PRN is an effective strategy if you see the patient every month indefinitely. But is that realistic? PRN is a reactive strategy, while the benefit of T&E is that you are always treating the patient. If you treat a recurrence of neovascular AMD with PRN, there can be irreversible vision loss and the patients may not regain the vision even with treatment. For example, in the second year of the VIEW studies,^{11,12,17} patients were managed with a capped PRN management strategy with monthly monitoring. The outcomes were still good at 2 years, but they lost a little bit of vision compared to the first year. A retrospective, post-hoc analysis of the second year showed about 20% of those patients lost more than 5 letters due to recurrences of fluid with the PRN

approach.^{11,12,17,18} Even with close monitoring, PRN allows for a dangerous recurrence of fluid.

Charles C. Wykoff, MD, PhD: I have learned from PRN trials that there is a proportion of patients with wet AMD that, once you get them dry, can remain dry for 2 to 3 years of follow-up with no additional treatments. If my patient has dried out after one or two injections, I might consider using a PRN treatment regimen with them. Sometimes you will treat a small choroidal neovascular membrane that responds beautifully to intravitreal injections and they do not need additional dosing. Unfortunately, my clinical experience, which reflects data from the published PRN trials, is that this proportion of patients is small. Overall, more than 90% of my wet AMD patients need ongoing dosing, in many cases indefinitely with current generation anti-VEGF therapies. And for those patients, the T&E approach is the most efficient. Patients receive significantly fewer injections over time compared to fixed monthly dosing with comparable long-term outcomes.

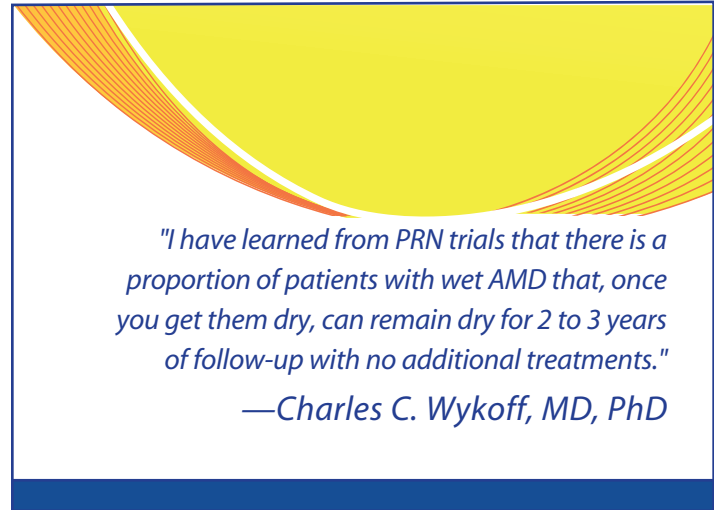
Dr. Clark: How do you define T&E in clinical trials? How does that differ from T&E in the real world?

Dr. Wykoff: The challenge with translating clinical research into clinical practice is that the criteria become much looser in the real world. The TREX and ATLAS trials showed that if there is any recurrence of fluid, then the interval is too long.^{10,13,14} When Dr. Regillo presented the ATLAS results, he commented that he has a “zero tolerance” policy for fluid, and I agree. I think a mistake that can be made in real-world practice is that one may have a tendency to start extending the intervals between treatments despite residual macular fluid because of injection fatigue either on the part of the doctor and/or the patient. In my own hands, I treat and extend, but I continue with monthly dosing until the macula is absolutely dry before I begin to extend the interval. If I see any recurrence of fluid when I extend the interval, I shorten the interval for the next visit.

SELECTING TREATMENT STRATEGIES AND INTERVAL LENGTH

Dr. Clark: How do you determine interval length?

Dr. Wykoff: It is situation and patient dependent. For example, if it is a monocular patient with a large lesion, then I will favor 1-week interval increases. In comparison, if it is a binocular patient with a smaller lesion with a relatively normal fellow eye, then I will typically start by extending in 2-week increments; after I get the macula dry at 4-week intervals, I will move to a 6-week interval, and so forth. As long as the macula remains dry, I will keep lengthening the interval gradually. Once there is recurrent macular edema, I typically will maintain the patient at a treatment interval just short of that interval. I rarely re-challenge this maximum tolerated interval in practice with the same medication. I rarely stop injecting at 12 weeks or go beyond 12 weeks, regardless of the medication.



"I have learned from PRN trials that there is a proportion of patients with wet AMD that, once you get them dry, can remain dry for 2 to 3 years of follow-up with no additional treatments."

—Charles C. Wykoff, MD, PhD

Jay S. Duker, MD: I perform individualized therapy. Most of my patients are getting T&E in order to find a reasonable, fluid-free interval, and I will stick with that interval long-term. I extend slowly, and do not generally take my injection interval out past 3 months. On the other hand, I have patients who I try to extend initially, and they end up with recurrent fluid at 5 or 6 weeks, and that interval becomes their fixed interval over the long term. I also have a handful of patients on a PRN regimen who can go 8 or 9 months between injections, have indolent type 1 choroidal neovascularization (CNV), and are perfectly comfortable with a PRN approach.

The CATT trial showed us that there are some patients with a little bit of subretinal fluid, particularly in patients with retinal pigment epithelial detachments and some type 1 membranes, who are never going to be completely dry, even if we continue to treat them monthly.^{8,19} If these patients have good visual acuity with just a sliver of subretinal fluid, I consider that a new baseline and I will often attempt to extend the interval off that new baseline carefully. But if I see that fluid increasing, then I am reverting to more frequent dosing.

Dr. Clark: What are some of the factors you consider as you are developing a treatment strategy?

Dr. Duker: I believe in an induction phase and a maintenance phase. For induction, I treat patients monthly until we reach maximum improvement, both anatomically and visually. If there are two consecutive visits where there are no further anatomic or visual improvement, that becomes the new baseline. At that point, we discuss the three options: (1) weekly T&E; (2) PRN; or (3) long-term monthly maintenance. My preference is a slow T&E. Some patients have difficulty coming in as often as I would like, so we compromise on a 2-week T&E. Others do not mind the appointments, but hate injections, so we will do PRN. I do not have a one-size-fits-all approach.

Dr. Clark: How have dosing methods evolved over the past 3 to 5 years, based on clinical research and published trial data? Have your attitudes about extending intervals or stopping treatment

changed? Do you have a sense of your overall treatment burden in your practice now compared with 3 years ago?

Dr. Regillo: We have learned a lot since anti-VEGFs first came on board more than a decade ago. It is now about fine-tuning and optimizing outcomes for our patients as we have gotten more comfortable with anti-VEGF injections. The term “fluid-free interval” is very appropriate. I like proactive treatment and the notion of continuous therapy. Drug durability will vary widely from person to person. Some patients have good VEGF suppression in AMD studies that equates to good disease control for as little as 26 days or as far out as 72 days.²⁰ Studies show that the disease-free interval is relatively consistent for a given patient. T&E is somewhat of a misnomer because over time, we do not always re-extend. I will sometimes sit at a specific interval with a patient because it is working well.

Recurrences are harmful because patients are potentially experiencing CNV growth (Figure 1) that may result in irrevocable harm. As CNV grows, additional tissue destruction may occur. We must prevent CNV growth and the associated signs of exudation. You treat during the induction until you get the macula as dry as possible. It may not always be dry, and some patients we can extend even with a little bit of fluid. But the goal is to make sure the CNV is not growing and, as Dr. Wykoff noted, I support a “zero tolerance” policy for fluid, if possible.

What I have learned over the past decade is how to balance these factors for the patient. Circumstances in the real world, like holidays or vacations, will sometimes force us to tweak a patient’s regimen. There is an element of guesswork. There is a lot of trial and error surrounding how to manage this disease on an individual basis. There is an art and a science to it.

Dr. Clark: One practice pattern that has changed for me during the past 3 to 5 years is that I am less likely to discontinue therapy. Early on when we first had anti-VEGF intravitreal injection therapy, I wanted to cure the disease and get people off treatment. What are your thoughts—have you been able to get your patients off treatment?

Dr. Wykoff: It is rare for me to discontinue treatment. The exception is a macula that dries out completely after few injections; I might try to discontinue

therapy in this situation. The other situation is a disciform scar; I might start therapy to see how much improvement we can achieve and if the patient has no benefit with treatment I might discontinue therapy.

If using T&E, I find that someone’s maximum fluid-free interval is 7 weeks, I will keep them there long-term. And if they are stable over time, eventually I may re-challenge this interval. In the TREX trial, we repeatedly re-challenged the longest interval.^{13,14} Although about 75% of patients were unable to stretch their maximum tolerated interval, 25% of patients were able to go longer upon re-challenge of their maximum tolerated interval.

I am not tolerant of subretinal or intra-retinal fluid, and I typically do not intentionally extend the treatment interval beyond a month in the presence of such fluid. My interpretation of PIER, CATT and HARBOR data is that patients have the best chance of optimizing their long-term vision if I continue to treat patients

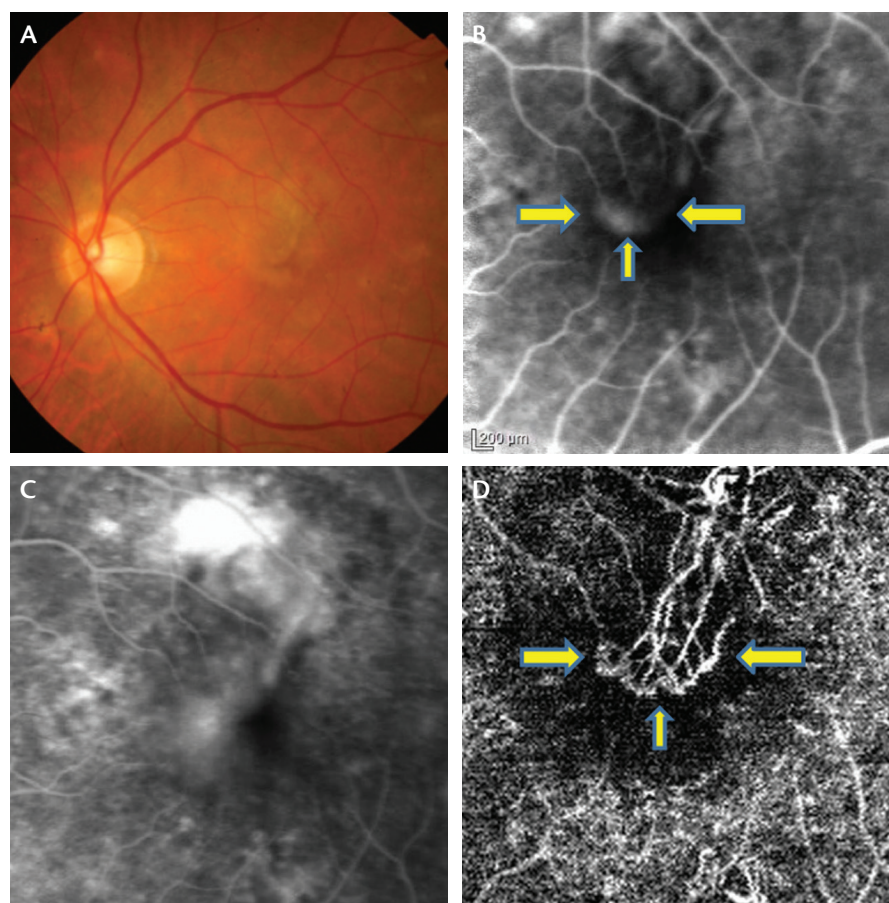


Figure 1. These images illustrate the eyes of a 72-year-old man who is pseudophakic in both eyes. Fundus photograph of the left eye shows greyish elevation of tissue deep to retina at macula suggestive of CNV in AMD (A). FA of the left eye shows a discrete, well-demarcated focal area of hyperfluorescence at macula (arrow) in early phase frame (B), with hyperfluorescence increasing in intensity in later phase frame (C) and extending beyond boundaries of hyperfluorescence identified in early phase, suggestive of classic CNV. The actual network of new vessels (arrow) can be very clearly delineated in OCTA, and its size corresponds to the extent of leakage from CNV seen in fluorescein angiogram (D).

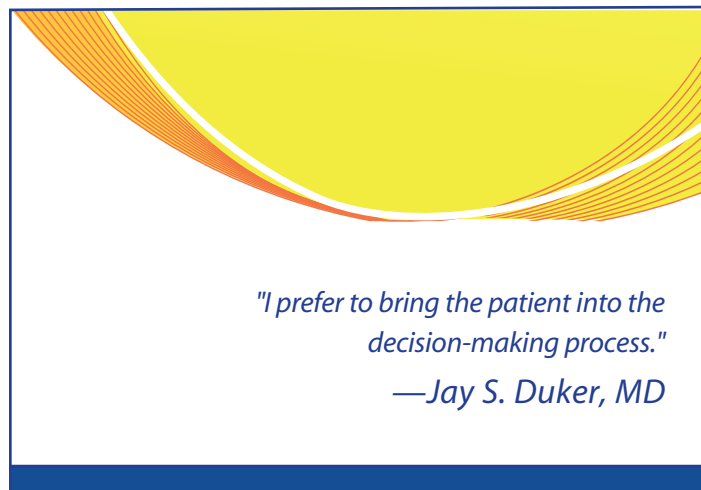
monthly in the presence of persistent fluid and avoid as many recurrences as possible once their macula is dry.^{8,9,19}

Dr. Clark: Is the overall treatment burden higher now than it was in the past?

Dr. Wykoff: I am certainly treating more aggressively today than I was 5 years ago, and I try to maintain that long-term. While we need more data, I am currently not concerned about causing macular atrophy through the appropriate use of anti-VEGF treatments when they are needed to control the exudative disease process; the data from CATT and HARBOR appear inconclusive regarding macular atrophy and how it relates to anti-VEGF dosing.^{8,9,19} There is more vision left on the table from under-treatment than from over-treatment.

Dr. Clark: There is a high incidence of bilateral disease in AMD. Do you have different approaches to managing the second eye of patients with wet AMD?

Dr. Khurana: It is safe to say I am much more cautious and sensitive with a monocular patient than I might be otherwise. But I do try to individualize treatment in the same manner. Chronic con-



ditions can be unpredictable, so patients must be monitored closely at a minimum if not regularly treated. Be very careful of extending too long between treatments. When I first started employing T&E management strategies, I would go out to 4 and 5 months. But then the second year of the LUCAS trial found that patients who were extended to 12 weeks had a higher rate of recurrence.^{21,22} Vision did not return after treatment. These results showed that a

Managing Patient Expectations and Noncompliance

Dr. Clark: If we have to choose one over the other, we all agree that overtreatment is more beneficial long-term than undertreatment. In the CATT trial,^{8,19} compliance issues may have played a role in some of those suboptimal results. My experience is that it is not difficult to get buy-in from patients with AMD if you educate them upfront. In your practices, how does patient compliance affect clinical outcome? Do you get pushback from patients when you encourage consistent, frequent visits?

Dr. Regillo: Not as much as you would think, especially if the patient looks at their own OCT. They will notice the fluid if you point it out. I think many patients understand that you are trying to keep the macula as dry as possible. We get our best results when this disease is caught early, when we minimize the recurrences, and when we keep the CNV small. If you make these points to the patient upfront—and can show them what you mean on their OCT—you are less likely to get pushback.

Patients like T&E because it usually leads to less frequent visits, and every encounter is predictable. They know they are there to get evaluated and to get treated, and there is no awkward pushback. With PRN, there can be pushback if the patient was hoping to skip a treatment and you have to deliver the news that they cannot. In general, the burden is the office visit, not the injection, and so patients typically prefer less frequent encounters coupled with the injection over monthly follow-up with intermittent, less frequent injections.

Dr. Duker: I prefer to bring the patient into the decision-making process. I prefer not to state unilaterally, "This is what we are going to do." Anecdotally, I have had patients tell me they have felt like the effect of the injection was wearing off a week or so before their scheduled visit. Often the examination and testing fails to confirm their impression. So I will ask if they want to go to 7 weeks instead of 8, and they typically choose to shorten the interval. This is a way to keep the patient engaged in the treatment paradigm.

Dr. Wykoff: I am clear with patients from the beginning that intravitreal injections can help, but they are not a cure. I have this conversation with patients and their family members repeatedly so we are all on the same page. I agree showing patients their OCT helps. But I do get quite a bit of pushback with patients asking if we can go longer between appointments. I keep them engaged by noting there are newer treatments being evaluated with longer intervals, but for the time being these are the best we have.

Dr. Regillo: The best outcomes come with keeping on top of signs of exudation, keeping our patients informed about their condition, and doing what we can to minimize compliance issues. Informed consent is an ongoing education process. It is important that we address patient questions and what needs to be done with every encounter.

10-week interval was safer with less recurrences when using ranibizumab or bevacizumab with T&E. Again, be careful when extending too long between treatments.

We conducted a sub-analysis of the HARBOR study and looked at the past duration as an indicator for future duration.²³ We found that past performance did not predict future performance.²⁴ Because the disease is so unpredictable, I would rather err on the side of overtreating than undertreating. The concern with recurrences is that you may have irreversible vision loss.

TOOLS FOR TAILORING THERAPY

Dr. Clark: Let us discuss patient subtypes. Analyzing fluorescein angiograms was of critical importance to treatment decisions before anti-VEGF therapy. Today, we “lump” them all together, treating anything with hyperfluorescence under the fovea. But most of us still have an interest in looking at the fluorescein angiogram (FA) and classifying the lesions. Do you use FA as a tool for tailoring initial therapy?

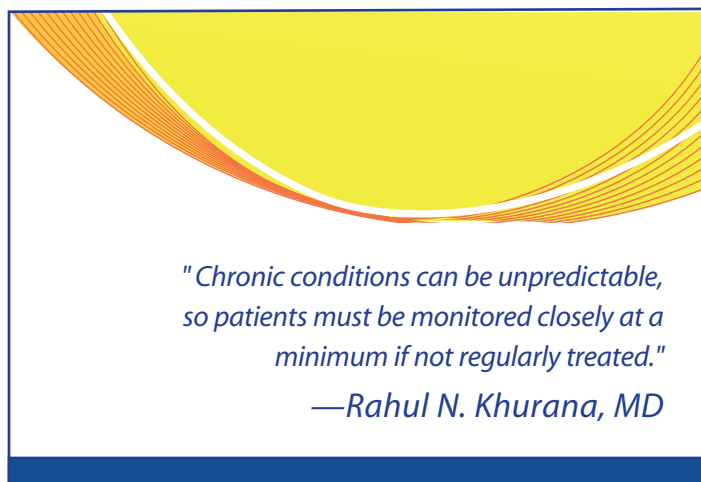
Dr. Khurana: I am a big believer in FA, and I think it is helpful for treatment decisions. I think issues come up if you are just using OCT to guide your treatment decisions. I will use FA at the initial diagnosis and before I start extending. It helps me decide when I want to extend and when we can go longer between treatments.

Dr. Clark: Can you tell which patients have lesions that require chronic, aggressive sustained therapy compared to the patients you may be able to extend relatively early in the course of treatment?

Dr. Regillo: I like using FA at baseline to confirm the diagnosis. I also like to see the size of a lesion because studies consistently show that small lesions have better outcomes in both absolute vision over time or vision gain, especially if the vision is decreased at baseline.²⁵ After treatment starts, I very rarely get an FA because it does not help me as much with treatment decisions. I think OCT angiography has the potential to be useful in the course of neovascular AMD treatment in select cases to get a quick, non-invasive look to see if the neovascular lesion is growing.

Dr. Clark: Do you change your approach to patients based on the morphology of the choroidal neovascular membrane? Is there a different approach to a patient with a retinal angiomatous proliferation (RAP) lesion versus a truly occult CNV, or are you initially treating patients the same and then moving forward?

Dr. Duker: I induce everybody the same way with monthly injections. But I make observations based on the angiogram, which I still get initially. There are two rare types of lesions that you can predict intensity of therapy ahead of time: extra-foveal CNV and early RAP lesions. If you can treat an extra-foveal CNV with anti-VEGF therapy when the lesion is small, sometimes the lesion does not recur for a long time, if ever. RAP lesions are exquisitely sensitive to anti-VEGF therapy before they have made the connection into the choroid.^{26,27} Those you can shut down and sometimes go



many months between injections. But neither of these lesions are common in my practice.

I do a lot of OCT angiography. Right now it is a great modality to detect the presence of CNV. The future is promising, but we do not currently have enough data on OCT angiography to use it as our sole guide to treating patients.

Dr. Wykoff: I have the occasional rare patient who can go out to 12 weeks and appear dry; I use FA most often on those patients. I will repeat the FA and compare it with baseline. If there is really no evidence of the lesion or definitive leakage, then I might switch from maintaining at quarterly dosing to PRN re-treatment. I do not typically use FA routinely when I am doing standard T&E because I am basing most of my decision on my OCT findings and ophthalmic exam.

Dr. Clark: To make a diagnosis and initiate therapy, we need an initial FA, OCT, and a clinical exam. But how do you use imaging in the treatment phase? Do you have a basic strategy or pattern?

Dr. Khurana: I use FA more than others because I have found there can be a disconnect between what you see on FA and what spectral domain OCT seems to tell us. Let us take the example of occult lesions, where we know we are going to need more treatment. There is good sensitivity with these imaging devices,²⁸ but they are not perfect. There are some cases of occult CNV that are “dry” on OCT but have leakage on angiography.²⁸ I am concerned about undertreatment if you are just using OCT, which sometimes do not detect fluorescein leakage, especially for occult lesions. A “dry” OCT may give us a false sense of security, especially if we are only using that information to extend intervals or withhold treatment. I have also been surprised when the OCT is dry but the CNV lesion has enlarged on angiography.

Regarding macular atrophy, obtaining autofluorescence annually or even every other year is helpful to monitor atrophy. It is helpful to supplement the standard OCT with autofluorescence and FA throughout key time points as you are following these patients over time, considering extending intervals between treatments

and or if there is severe vision loss not explained by the OCT. AMD is a chronic disease and having different sets of imaging is helpful as you monitor these patients over time.

Dr. Clark: What is the role of indocyanine green angiography in the age of anti-VEGF therapy?

Dr. Regillo: I very rarely ever get an ICGA at either presentation or in follow-up for neovascular AMD. If there is something unusual happening (for example, if the patient has been doing well and maintaining vision but then inexplicably starts to complain about vision loss), I will do a follow-up FA or OCT angiogram—something in addition to a standard OCT to determine what the cause is, and whether I still have control of the exudative process. If I start to see atrophy, I will follow-up with fundus autofluorescence intermittently to see if that is changing or to better define the location of the atrophy relative to the fovea. ICGA does not usually add anything that is clinically useful to these other tests in the course of treatment.

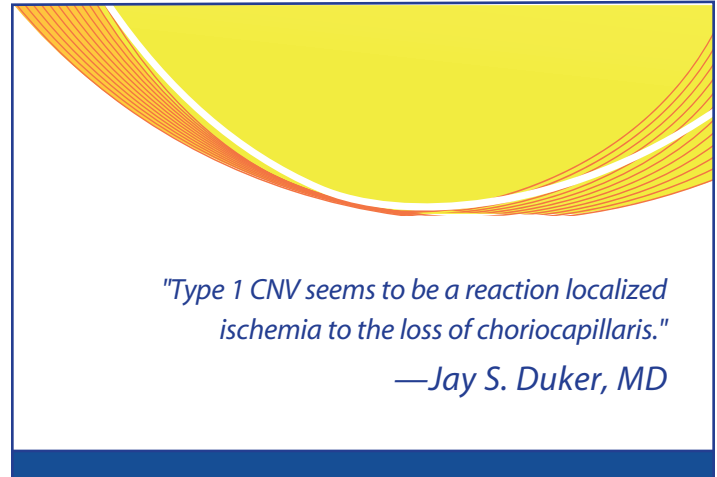
Dr. Clark: Visual acuity is of primary importance to the patients and regulatory bodies as it pertains to clinical trials and drug approval. How do you analyze visual acuity in your practice? How do you integrate that data into the management of a patient's disease with T&E?

Dr. Wykoff: I use four things to assess how a patient is doing and guide my treatment: patient symptoms, imaging, examination, and Snellen acuity. The most important is the patient's symptoms followed close behind by imaging. If they come in and say that their vision is fine with no change but the Snellen acuity went from 20/40 to 20/60 and the OCT looks stable, I tend to ignore the Snellen acuity.

Dr. Khurana: Symptoms are very important for patients, but it is not my primary parameter. Snellen visual acuity is a helpful surrogate, but it is too subjective and unpredictable. It is often not consistent with the exam or imaging findings, so it is one of our second-tier parameters when monitoring disease. There is, however, a great deal of value in seeing how patients progress over time. When they have vision improvement early on, it keeps them engaged but also means they are going to be a bit more hypersensitive when that vision starts to deteriorate again.

Dr. Clark: How should we bring OCT angiography into clinical practice? Should we use it as a standalone tool or in conjunction with FA?

Dr. Duker: OCT angiography is an excellent tool for diagnosing the presence of neovascularization, whether it is retinal neovascularization from diabetes or sub-retinal CNV from any cause. OCT angiography can tell us if the eye is vascularized right away in most cases. We do not need to do an FA unless there is a reason to subtype it or if we want to see leakage. OCT angiography is also really



helpful to show type 1 neovascularizations, which often features flat, irregular retinal pigment epithelial (RPE) detachment on OCT cross sectional images. These occult or type 1 vessels are usually much larger than what is seen on FA, and the areas that leak are the edges. There is high-flow mature vessels in the center of these large sub-RPE NCV, and about 75% of these type 1 membranes have one or two central trunks, which are not VEGF-responsive.²⁹ It is the fringe areas that are treatable and will show flow reduction after anti-VEGF therapy.

We need more research on CNV to understand why it forms, but type 1 CNV seems to be a reaction localized ischemia to the loss of choriocapillaris,³⁰ which is one of the first things that occurs in both dry and wet AMD. So far, we have been unable to reliably tell if a CNV is active or inactive based on OCT angiography alone. Cross-sectional OCT, clinical examination for hemorrhage, and talking to the patient still surpasses OCT angiography. In the future, I think we will be able to volumetrically quantify these CNVs, but that is still a couple of years away.

Dr. Regillo: OCT angiography is still in its infancy, and we are still learning what it can do and what it can tell us, and how that may influence how we treat. I have found OCT angiography to be potentially useful in select clinical scenarios, such as chronic atypical central serous chorioretinopathy when there is the suspicion for secondary neovascularization.

Dr. Wykoff: We are still evaluating its clinical use as a field, but currently I am using OCT angiography primarily in the context of prospective clinical research. Occasionally, if there is a case where it is unclear if there is choroidal neovascularization on FA and OCT, I will use OCT angiography. In my hands, though, the current generation segmentation algorithms are not as good as I would like.

Dr. Clark: Is it a matter of time before OCT angiography supplants FA in routine retina practice?

Dr. Duker: I think macular FA is on its way out the door. It is

hard for me to convince early-career retina specialists that they need to do an FA for diabetic retinopathy or CNV membranes because the angiograms seem to add little to the treatment regimen and certainly interfere with clinic flow and efficiency. Using cross sectional OCT and OCTA, we have the ability to image and diagnose abnormal vasculature with a single test; and we have to send the patient back to the photographer for a dye-based test that is going to take an additional 45 minutes. Peripheral FA is still important in some diseases, and we are still several years away from wide-field OCT and widespread OCT angiography use. But when that happens, FA will be dead.

ESTABLISHING LONG-TERM TREATMENT PLANS

Dr. Clark: What is the long-term treatment plan for wet AMD? How do you use personalized disease management to reach disease-free intervals in most patients?

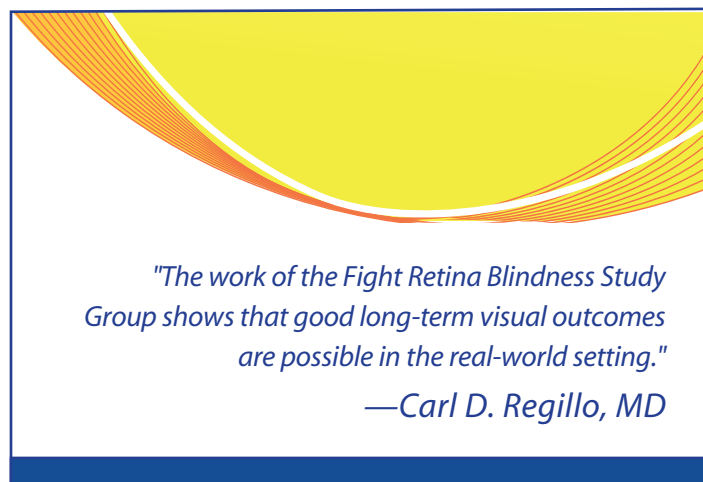
Dr. Regillo: It is about using everything at your disposal to get the best vision gains and maintain them over a long time. It is about talking to each patient about trying to keep the macula and their vision as good as possible by keeping on top of the signs of exudation and stressing compliance to the recommended follow-up visits.

As I mentioned earlier, the work of the Fight Retina Blindness Study Group shows that good long-term visual outcomes are possible in the real-world setting.³¹ This contradicts the 5-year CATT data.⁸ There is definitely an element of relative undertreatment in the 5-year CATT follow-up study along with other studies that show the lack of maintaining the vision gains beyond 2 years or so into the course of treatment.

Dr. Khurana: The 5-year CATT data were helpful for a lot of reasons. Five years after being diagnosed with this blinding condition, 10% of patients were 20/20 or better, and 50% of patients were 20/40 or better. But the vision gains that they achieved in the first 2 years were lost by 5 years, 80% of patients had fluid on OCT, the CNV lesions grew on FA, and 20% were 20/200 or worse despite an injection about every 10 weeks.⁸ That tells me we are still under-treating our patients.

Long-range data shows that the more you treat the better your patients do. Sometimes we are lulled into a routine where the OCT looks dry, we give an injection, and think everything is going well. But over time, there is a gradual loss of vision. Sometimes the OCT gives us a false sense of security. We have to have a low tolerance for any type of fluid, and we need to maintain fixed dosing for patients long-term to maintain as much vision as possible. The RANGE study showed good outcomes with regular treatment under tight intervals.^{32,33} I still do not think we are treating enough to maintain the vision that we initially gained in the induction phases, and early on in the treatment of the disease.

Dr. Clark: The TREX AMD trial demonstrated that T&E protocol was equivalent to monthly therapy out to 2 years with a reduced treatment burden.¹⁴ It is a great example of what can be



done with meticulous follow-up. Is that level of follow-up realistic in everyday clinical practice?

Dr. Wykoff: It is very easy to fall into the trap of under-treatment, which will lead to a gradual vision decline over time. The PIER study³⁴ was the original great example of this. We saw an initial "wow" effect with the monthly loading doses, and then when patients were switched to quarterly dosing, they slowly regressed to baseline over the rest of the year. I do think it is important to be aware of fluid and to go after it. Study after study points toward more frequent dosing being associated with better visual outcomes at a population level.^{8,14,23,31,34} It is difficult to do that in the real world for many reasons.

Dr. Duker: There are reasons that these patients lose vision besides recurrent fluid. I think it is dangerous to put a blanket across everything and say, if you are only doing five injections a year, you are under-treating. There are some people who can do very well in the long term with fewer injections. The key is to identify the patients who need frequent injections and keep the intensity up long term while providing individualized therapy with input from patients and their families that enable the clinician to select out the eyes that can do well with less frequent intervals. The interval decisions are often made individually and communally and not just from a one-size-fits-all evidence-based study. But overall, it's best to err on the side of overtreatment. If you have any doubts, if the patient is losing vision, if you are seeing any sign of CNV activity, treat the patient and shorten the interval.

GEOGRAPHIC ATROPHY AND OTHER SAFETY CONSIDERATIONS

Dr. Clark: What are some thoughts on the long-term safety considerations of therapy? What is the association between geographic atrophy (GA; Figure 2) and anti-VEGF therapy?

Dr. Regillo: I am not convinced GA is from frequent anti-VEGF therapy. Rather, I think it is more likely to stem from natural dry disease progression and, maybe also influenced by presence of

CNV and associated exudation that typically resolves with anti-VEGF therapy. Unfortunately, we will never know for sure. If GA is somehow exacerbated by frequent anti-VEGF treatment, then it makes sense adhere to the dictum of just enough treatment to achieve the best visual/anatomic results and avoid over treatment. That being said, based on what we know to date, I think that you are more likely to adversely affect the vision outcome in the long run if you withhold anti-VEGF therapy to some degree or under-treat the patient because atrophy is emerging in the course of therapy. Atrophy does play a role in long-term vision outcomes and some of the vision declines that we have seen in some studies.^{19,35-38} But more often than not, in wet AMD management, vision declines are due to relative under-treatment with either persistent/recurrent exudation and/or CNV growth.

Dr. Wykoff: Based on my interpretation of the limited data we have from CATT and HARBOR, I do not think that the appropriate clinical use of anti-VEGF injections makes a significant impact on the natural course of macular atrophy.^{8,9,19} Some analyses have suggested that, at a population level, monthly dosing may be associated with more macular atrophy than PRN dosing. Certainly more data is needed to further address this important issue. I do not think the current data should impact how physicians are using anti-VEGF agents in clinical practice. Most physicians in the United States and around the world use individualized dosing and in this context, the overwhelming majority of data supports treating any evidence of active exudative disease, because there is significant visual acuity to be lost if active CNV membranes are left undertreated.

Dr. Clark: Looking at emerging therapies in the treatment of GA, there is great interest in using anti-complement drugs in patients with dry AMD and geographic atrophy. What is their role in combined GA with exudative AMD?

Dr. Duker: As a founder of a biotech company developing an intravitreal gene therapy based anti-complement treatment for dry AMD, I am biased toward anti-complement therapy. However, there is substantial evidence that complement activation plays a role in both dry and wet AMD. If you block complement, whether it is membrane attack complex, complement factor C-3 or C-5 in laser models of CNV, you can reduce the CNV activity inside by 60% to 70%.^{4,39-43} That is about the same as anti-VEGF therapy. Anti-complement therapy is not going to be useful as an anti-permeability agent like anti-VEGF therapy. But there may be a role for combined therapy in wet AMD. Ophthotech is currently doing a phase 2 trial looking at combined anti-VEGF and anti-C5 for wet AMD.

Dr. Clark: I agree it would be a shame to suggest undertreatment of

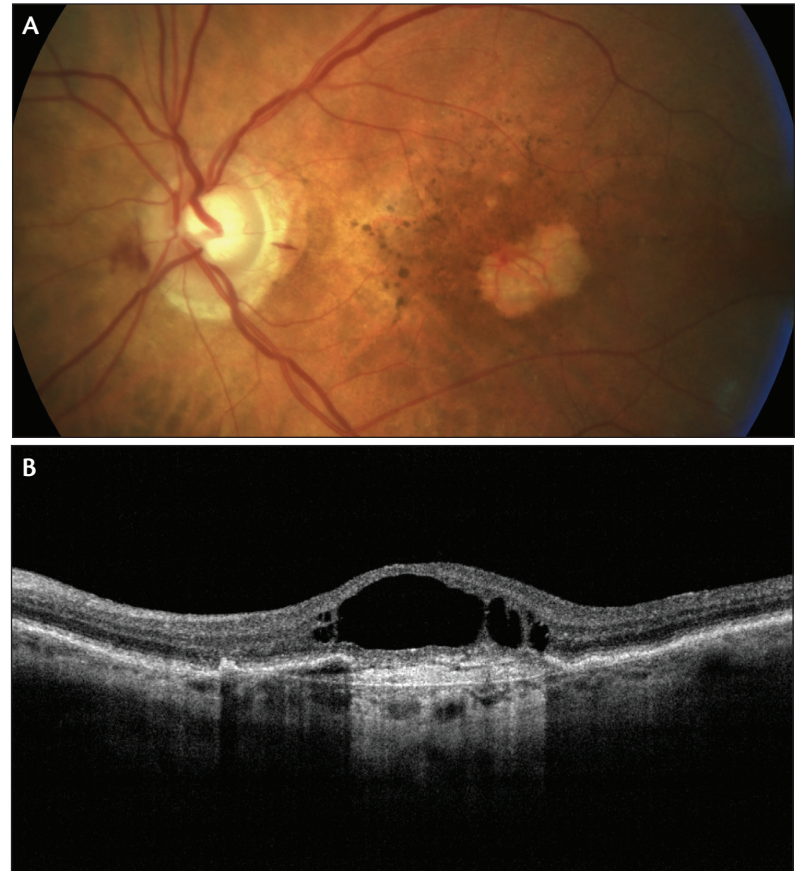


Figure 2. These images illustrate a patient with both exudative and nonexudative AMD. Fundus photography and OCT reveal a hint of glaucoma and a Drance hemorrhage at the nasal margin of the optic nerve (A). Macular degeneration with drusen and areas of focal hyperpigmentation were noted in the macula, as was a zone of juxtafoveal GA. OCT showed a large cystic area overlying the GA (B).

exudative disease at the expense of concerns about GA.

Dr. Duker: The CATT trial discussed atrophy, but it did not specifically look at GA.^{8,19} CATT looked at overall retinal thinning and retinal atrophy. Sometimes we use these two concepts interchangeably. In saying that, there are certain lesions that we know have a high rate of GA—RAP lesions are one example. The patients almost invariably get well-demarcated atrophy in the areas of the type 3 CNV. those lesions out. But there are type 1 CNV lesions where atrophy does not occur even after years and dozens of anti-VEGF injections. So, I do not think we should undertreat patients for the potential fear of atrophy, especially when we have got the real fear of fluid in active wet AMD.

I think a combination therapy may be the answer in the future. Of course, we will need to consider patient burden as it would be difficult for some patients to receive monthly or bi-monthly injections of two drugs forever. But perhaps we will have a slow delivery system that would allow us to hit multiple pathways and not only stop the exudation and keep the choriocapillaris intact, but stop the atrophy as well.

"I have occasionally gone from continuous, T&E approach to a PRN approach for a patient who has had a recent severe, debilitating stroke. But I can count on one hand how many times I have significantly altered management."

—Carl D. Regillo, MD

Dr. Clark: Looking at these clinical trials, are there any safety signals, ocular or systemic, that are concerning? Should we feel comfortable treating these patients aggressively with anti-VEGF therapy?

Dr. Khurana: When you look at the totality of the evidence from all the clinical studies, the safety profiles of the drugs in our armamentarium are impressive.^{7,44,45} From an ocular and systemic perspective, we have always seen little things pop up regarding systemic safety. But, in totality, I do not think there are any trends that should set off a warning. As a retinal community, we must always be vigilant for any adverse events that may occur and share that information freely. Recently, there has been concern with intraocular pressure over time with repeated treatments.⁴⁶⁻⁴⁹ We should continue to monitor and accordingly treat this as it occurs. However, as a whole we should feel very comfortable with the treatment options.

Dr. Clark: Do you recommend modifying treatment in patients with known cardiovascular disease or recent events?

Dr. Regillo: For the most part, no. I will certainly discuss with the patient the theoretical possibility of a cardiovascular or cerebrovascular event. I have occasionally gone from continuous, T&E approach to a PRN approach for a patient who has had a recent severe, debilitating stroke. But I can count on one hand how many times I have significantly altered management. ■

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

1 AMA PRA Category 1 Credit™

Expires June 2018

1. If a patient with neovascular AMD has a recurrence of fluid or CNV activity while on treat and extend treatment regimens, you should _____.
 - a. Extend the interval
 - b. Shorten the interval
 - c. Discontinue treatment
 - d. Continue maintenance therapy
2. Please rate your confidence in your ability to evaluate and compare the safety and efficacy of different dosing strategies (eg, monthly treatment, TAE, PRN)? (Based on a scale of 1 to 5 with 1 being not at all confident and 5 being extremely confident.)
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
3. Agree or disagree: Aggressive anti-VEGF therapy has a substantial impact on macular atrophy progression in patients with AMD and should be avoided.
 - a. Yes, the data are conclusive
 - b. No, macular atrophy is tied to under-treatment
 - c. Data are inconclusive
4. OCT angiography alone is most useful to diagnose all conditions listed *except* _____.
 - a. Chronic atypical central serous chorioretinopathy
 - b. Vascularization in type 1 vessels
 - c. Choroidal neovascularization
 - d. Geographic atrophy
5. _____ trial demonstrated that treat and extend protocol was equivalent to monthly therapy out to 2 years with a reduced treatment burden.
 - a. CATT
 - b. TREX
 - c. HARBOR
 - d. PIER
6. When should you potentially modify treatment of patients with cardiovascular disease?
 - a. You should not; cardiovascular disease is an irrelevant comorbidity
 - b. Only in patients with a stroke event in the previous 3 months
 - c. Only in patients with a stroke event in the previous 2 years
 - d. You should always modify treatment in a patient with any known cardiovascular disease or cardiovascular event
7. _____ of type-1 membranes have central trunks that are not responsive to anti-VEGF therapy.
 - a. 25%
 - b. 50%
 - c. 75%
 - d. 85%
8. Please rate how often you intend to apply outcomes of pivotal AMD studies to "real-world" patient assessment, diagnosis, treatment, and management (based on a scale of 1 to 5 with 1 being never and 5 being always):
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
9. Indicate which statement(s) is(are) true.
 - a. Undertreatment is better than overtreatment in neovascular AMD
 - b. Anti-VEGF treatments do not pose significant systemic threats
 - c. OCT angiography should not be used as a sole determinant of disease progression
 - d. Studies have shown no clinical or statistical difference between monthly, PRN, or treat and extend dosing regimens in terms of visual outcomes in neovascular AMD
 - e. Vision gains after anti-VEGF injections in neovascular AMD are permanent.
10. Based on evidence from clinical trials, which of the below individualized dosing strategies for anti-VEGF treatments has been shown most effective?
 - a. Monthly treatment
 - b. Treat and extend
 - c. PRN
 - d. None of the above

ACTIVITY EVALUATION

Did the program meet the following educational objectives?

Agree Neutral Disagree

Discuss the outcomes of pivotal studies in AMD, and how study results may differ from “real-world” dosing methods.

Identify patient subtypes (eg, RAP lesion, pigment epithelial detachments, occult lesions) that will require long-term treatment and imaging evaluation

Develop a long-term treatment plan for patients with AMD based on results from clinical trials and extension studies.

Compare the extended safety outcomes of anti-VEGF therapies as published in long term studies.

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).

Name and email: _____

Do you feel the program was educationally sound and commercially balanced? ☐ Yes ☐ No

Comments regarding commercial bias:

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

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

Would you recommend this program to a colleague? ☐ Yes ☐ No

Do you feel the information presented will 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 the 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: _____

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