AMD in 2016: A Review of Treatment Guidelines and the Role of Early Appropriate Therapy

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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:
• Assess 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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AMD in 2016: A Review of Treatment Guidelines and the Role of Early Appropriate Therapy

A roundtable discussion about current treatment guidelines and an examination of the clinical relevance of clinical trials data.

Retinal disorders, including age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO), can result in vision loss if not treated early and, in some disorders, continuously. Significant challenges lie ahead in addressing these patients’ needs, as the impact to society in both direct and indirect costs cannot be overlooked, and health care providers are being tasked with treating increasing numbers of patients. Findings from major studies support the use of anti-VEGF agents as first-line therapy because they have been shown to improve vision-related quality of life. This roundtable discussion examines the importance of early therapy, the use of and responses to anti-VEGF agents for AMD, the effects and expectations of anti-VEGF therapies in the real world versus clinical trials, and the implications surrounding new therapies.

—Allen C. Ho, MD

Allen C. Ho, MD: We are now 10 years into an anti-VEGF treatment paradigm for wet AMD with several choices of VEGF inhibitors. Where do you see us going in terms of improving our therapies? Can we raise the bar with the new drugs? If so, how far can we expect to go?

Darius M. Moshfeghi, MD: I think the key will be to increase the durability of effect. I doubt we will see huge improvements in patients’ visual acuity, because many of our patients present with relatively good vision. Most of my new wet AMD patients are initially 20/50 or better, giving us a good chance at providing useful vision. With ranibizumab, I injected patients monthly. I inject patients every 4 to 8 weeks with aflibercept.

Justis P. Ehlers, MD: Future opportunities for new therapies include continued improvements in visual acuity outcomes, but in particular we are searching for increased durability of effect to decrease treatment burden for patients.

Dr. Moshfeghi: Most of my patients are not reluctant to come to the office for injections on a regular basis, because treatment provides an immediate improvement in visual acuity, and because they tend to be highly educated and highly motivated.

John D. Pitcher III, MD: I treat a more heterogeneous population, but my patients have the same expectations that Dr. Moshfeghi described. Ten years ago, patients had limited options and did not respond well because they were already fibrotic by the time we provided treatment. Consequently, everyone involved developed a pessimistic outlook. As a new vitreoretinal specialist, I find myself fighting patients’ negative feelings. I assure them that the future is brighter since we have more options.

I do not think that there is a total ceiling effect. In the registration trials,1,3 30% of patients gained less than 5 letters. I think there is an opportunity to increase efficacy as well as duration of treatment in those patients.

Dr. Ho: Dr. Ehlers, you are quite involved in clinical research at the Cleveland Clinic and we have all witnessed and participated in the search for better wet AMD therapies. Has it become more difficult to recruit patients for clinical trials because of the large number of new clinical trials for wet AMD?

Dr. Ehlers: In some cases, yes. The trials of therapeutics that are hoping to improve on our current visual acuity outcomes often have quite stringent visual acuity inclusion criteria, which can make finding eligible patients more difficult. With earlier detection, many
patients are coming in with excellent visual acuity. I have not seen a lack of patient enthusiasm for new clinical trials as an issue. Most patients have someone they know who has received ongoing regular injections. This creates significant motivation for some patients to participate in clinical trials.

Dr. Ho: Dr. Busbee, you published the 1-year data report in the HARBOR study. Do you think this will raise the bar for our patients with wet AMD?

Brandon G. Busbee, MD: That depends on whether you are talking about vision increases or duration of effect. I was a big believer in small trials. Many subjects were super-responders, and we had not yet fully developed the treatment curve in 0.3 mg versus 0.5 mg ranibizumab for AMD in the ANCHOR and MARINA studies. It was compelling that we progressed to a phase 3 trial and examined treatment with 2 mg and 0.5 mg ranibizumab. We found that although there were super-responders, the effect was diluted because everybody did really well, even at a lower dose.

Dr. Ho: What do you mean by super-responders?

Dr. Busbee: With standard dosing of any anti-VEGF, patients have a ceiling of response. When you increase the dose, some patients have a letter jump and also an increase in the duration of effect. The HARBOR study confirmed that standard 0.5-mg dose ranibizumab is effective. I regret, however, that a subgroup of patients never reach the ceiling because I do not have the 2-mg dose to offer them. The other problem is identifying that subgroup of patients who will respond. Phenotypically, these are patients with pigment epithelial detachment or subretinal fluid at baseline. These patients also generally see well and respond better with higher doses or higher concentration of drug.

Unfortunately, in the clinical setting, we cannot duplicate the improvements in vision that occur in the registration trials. The best responders in my practice are those who have gone through investigator-sponsored trials with strict protocol-driven treatment criteria. Some of these patients went through small clinical trials and maintained their vision even better than demonstrated in the SEVEN-UP study.

Dr. Ho: Our discussion seems to be centered on visual acuity gains as we follow this group of AMD patients beyond 2 years. Is this a function of treatment burdens? Are patients not getting better because they are tired of coming in for therapy? Also, what other treatment options for wet AMD do you use?

Dr. Pitcher: Since I started practice a year and a half ago, I have not used photodynamic therapy (PDT) for wet AMD. I use only the anti-VEGF options.

Dr. Busbee: My first option is also anti-VEGF treatment. My second option is to offer patients enrollment into a clinical trial.

Dr. Ehlers: I initially inform patients about opportunities for any clinical trials they might be eligible to participate in. Otherwise, I start with one of the anti-VEGFs and, if that fails to produce effective results, I will switch to another anti-VEGF. I usually reserve combination anti-VEGF/PDT first for patients with polypoidal choroidal vasculopathy or central serous-type variants with choroidal neovascularization (CNV). For wet AMD, anti-VEGF therapy is certainly first line.

Dr. Ho: Let me present a case example to our panel. A 77-year-old woman, who is 20/30, has macular drusen and dry AMD as well as a mild cataract in her left eye. She recently noticed new blurring gains as we follow this group of AMD patients beyond 2 years. Is this a function of treatment burdens? Are patients not getting better because they are tired of coming in for therapy? Also, what other treatment options for wet AMD do you use?

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of vision in her right eye. She has some hemorrhage, macular drusen, and thickening with subretinal fluid and intraretinal fluid on optical coherence tomography (OCT) (Figure 1). Before we choose an anti-VEGF, let us discuss the differential diagnosis and what your imaging and management approach might be.

**Dr. Moshfeghi:** This patient comes in with drusen and fluid that I can see both clinically and on OCT. I might get a fluorescein angiogram (FA) at baseline to confirm it. But basically I will say this is macular degeneration unless I see a cotton wool spot or something unusual with a blood vessel. I will go with the easy diagnosis and offer an anti-VEGF, probably that day, and then I will bring her back in 4 weeks. My general strategy would be to make the diagnosis, treat, give three injections in a row then re-evaluate the situation.

**Dr. Busbee:** I would treat this patient as an AMD patient; however, I would get a baseline FA, because I like to see what I am starting with. If I do not achieve the desired outcome, I will repeat the FA. I actually underutilize FA because we are so busy, but it is a helpful tool, especially to help you determine whether switching therapy is an option. It also helps to determine what the current problem is, for example, leaking or just an anatomic variation on OCT.

**Dr. Moshfeghi:** My clinic is somewhat resource-constrained. We have only two photographers on the retina service, and if you put every patient through FA, you are not likely to get your OCTs.

**Dr. Busbee:** I use FA on 100% of my patients.

**Dr. Moshfeghi:** I use it on 15% of my patients.

**Dr. Ehlers:** From an academic standpoint, it would be nice to have an FA on any new wet AMD patient. From a treatment standpoint, in most cases I do not think it is necessary. OCT angiography (OCT-A) is also an emerging diagnostic that provides new insights on flow information without the logistics of a dye injection (Figure 2). I find that I am using OCT-A more frequently in these patients.

**Dr. Busbee:** I go one step further. If someone has intraretinal fluid, I get a baseline fundus autofluorescence.

**Dr. Moshfeghi:** VIEW I and VIEW II provided data on angiogenesis, where we looked at the four possibilities of fluorescein leakage and fluid presence. It turns out that if 95% of patients at baseline have leakage and fluid after 12 consecutive injections at 52 weeks—whether they are receiving ranibizumab or aflibercept—the pool of patients will have been reduced to about half. But if you look at what happened in year 2, which provided a capped as-needed (prn) treatment, the half who had no leakage and no fluorescein got the minimum mandatory number of injections versus all the other groups, which had as many as 6.9 injections. We are all too quick to declare failure after only three or four injections and then switch drugs. But how do we know when that failure will occur? Based on these data, I would use FA and my OCT data to determine which of my patients might be better off receiving more injections to maintain vision.

One of my complaints with the current treat-and-extend modality is that treatment occurs late. We treat after the choroidal neovascular membrane is established. Fluid and leakage and decreased vision are lower priorities on the timeline, but the development of choroidal neovascular membrane can be tracked with OCT-A early on. OCT-A raises the potential of a better treat-and-extend outcome. Based on published data, I might want to evaluate my patients with fluorescein OCT after 52 weeks to see whether they might be candidates for treatment further out.

**Dr. Ho:** I like that you used the word “potential” with OCT-A. We are all in the learning phase of understanding how OCT-A will help us in diagnosis and management of macular disease. To use it in the differential diagnosis of someone who has drusen or drusen with some cysts on OCT and no subretinal fluid or hemorrhage, I would be guided by the patient’s symptoms.

We need to be aware that an FA sometimes can help us make a diagnosis of wet AMD in the presence of a mimicker. The most common mimicker of wet AMD that I see is an adult vitelliform lesion that has some pigmented epithelial elevation and maybe some cysts in the neurosensory macula.

**Dr. Ehlers:** Those are the cases where I think OCT-A can be helpful.

**Dr. Moshfeghi:** Sometimes vitelliform lesions look more like CNV because of the pooling of fluorescein.

**Dr. Ho:** I think we all agree that prompt treatment of wet AMD is a priority. It is very time-sensitive compared with RVO and DME. Now comes the issue of deciding which anti-VEGF agent to use. We have anti-VEGF treatment options. Which would you choose on day 1?

**Dr. Pitcher:** For the average patient, I would recommend initial treatment with bevacizumab, which is an off-label use. After making the diagnosis and counseling the patient, I would bring the patient back within a week for an injection appointment, where we check vision and pressure but do not perform imaging. I then repeat this
Dr. Busbee: My first choice is always an on-label drug, if I can get access to it. If I cannot get access because of some problem with an insurance plan, for example, I use the sampling program. I think both ranibizumab and aflibercept work very well. I usually start an on-label anti-VEGF drug and monitor patients with OCTs at every visit and look for clinical signs of improvement. Although we have a lot of information about retinal disease, merely injecting an eye dumbs down the process. I try to understand what is going on. Consequently, I do more testing.

Dr. Ehlers: I usually start with bevacizumab and treat the patient on the same day. In our practice, we require prior authorization inquiry on every patient, except for those on standard Medicare. I think waiting a week for branded drug approval is far outweighed by the benefits of treating patients immediately. I use an imaging approach similar to Dr. Busbee’s. I want to see how patients respond, how the speed of their response correlates with their visual acuity, and see if they are totally dry after one injection.

Dr. Busbee: I would like to add one thing about the use of OCTs. Our job is to keep our patients engaged during a protracted period of chronic anti-VEGF therapy. When patients become disillusioned and feel that their vision has not improved, I show them the OCT results to illustrate their improvements and reinforce the value of therapy.

Dr. Ehlers: I agree. I always show my patients the results of their OCT. It increases their understanding that while this might be a long-term process, it is not a futile one.

With regard to drug choice, I think it is important to also recognize the source of your drugs. For example, we internally compound all of our bevacizumab at the Cleveland Clinic. This helps raise the level of trust in the drug and the process. Without a trusted source, I would have a different approach to the use of bevacizumab.

Dr. Ho: If you did not have access to a trusted compounding source of an off-label drug, would you change your choice?

Dr. Ehlers: If I did not trust my source, I would seek another source.

Dr. Busbee: The problem is that we typically do not know our sources personally. This, of course, brings another variable of risk when it comes to the patient’s vision. I am not willing to accept that if the patient’s insurance is willing to pay for a Food and Drug Administration-approved drug.

Dr. Ehlers: Absolutely. The patient’s interest must come first.

Dr. Ho: Those who advocate off-label usage find that bevacizumab has been given more attention than any of the on-label drugs; however, large databases show that event rates for endophthalmitis between the anti-VEGFs are similar; on the other hand, we are not aware of fungal or bacterial endophthalmitis outbreaks associated with on-label drugs; so, let the user beware. Dr. Moshfeghi, what is your initial choice of drug for a new wet AMD patient?

Dr. Moshfeghi: My choice is guided by my experience and training. Before my current position as a retina specialist, I practiced ocular oncology and trained at St. Jude Children’s Hospital, where we did a lot of retinoblastoma. This experience informed my adherence to regimens. A child with retinoblastoma must undergo a 6-cycle chemotherapy regimen. Even though the tumor shrinks in cycle 1, we follow the protocol completely. Similarly, the registration trials go out 24 months, during which time patients receive injections either monthly or two injections every 8 weeks. Consequently, I rarely let OCT results sway me from the regimen. I remain adherent to the prescribed regimen, despite OCT results. If you believe the data, you go with it.

Now we are getting data from follow-up studies. I prefer starting with aflibercept; I do three injections, get an OCT, and then I send them out every 8 weeks. Based on the literature, only about 10% of patients go out longer than 12 weeks. The intervals range from 4 to 10 or 12 weeks. With aflibercept, I can take most of my patients to 8 weeks. About 20% of my patients are on ranibizumab, and I have been able to get some of them out to 6 or 8 weeks.

Dr. Ho: Would you say then that you use a treat-and-extend approach with aflibercept as your first choice?

Dr. Moshfeghi: No, I do not use a treat-and-extend approach as my first choice, although I do prefer to have all of my patients on aflibercept because of the improved durability. I rarely get OCTs on my patients because OCTs were not used to guide therapy in the registration trials; however, they do help to keep the patients on board from an educational perspective, and they are useful in evaluating the second eye in patients with unilateral disease. I usually get an OCT every 6 months, making me one of the lowest utilizers of OCT on a per capita basis. Nonetheless, my patients gain vision and maintain it.

Dr. Ho: In this panel, we have two bevacizumab first users and two on-label drug first users. I myself am an on-label user first because the on-label drugs tend to do a little bit better in all the clinical trials. Although there are no good head-to-head studies between bevacizumab and aflibercept in wet AMD patients, the evidence with regard to efficacy leans toward on-label drugs. Tens of millions of patients have received bevacizumab injections, but the variability in drug dosage in a compounded syringe is a concern for me. What are your treatment methods after the initial few months?

Dr. Ehlers: I use a modified approach and typically use monthly
injections—whether I am using bevacizumab, aflibercept, or ranibizumab—until the patient is dry. I will then frequently give patients a trial of prn therapy. If they recur frequently or with significant fluid or vision loss, I convert them to a treat-and-extend regimen.

**Dr. Ho:** If your patient is dry after three injections, what would you do in the second eye of a patient with a disciform scar?

**Dr. Ehlers:** It depends on what their presentation was in that eye. However, in monocular patients, I usually strongly recommend a treat-and-extend regimen.

**Dr. Moshfeghi:** I, too, have begun moving toward a treat-and-extend regimen with a caveat: I am not willing to extend beyond 12 weeks. Bear in mind, I rarely move anyone to a treat-and-extend regimen until after a year.

This goes back to defining what failure is. If you go back to the MARINA study, no patient gained 3 lines of vision after month 12, but you could have gained 3 lines of vision at the eleventh injection. So how can you deem treatment a failure unless you have given the full regimen of 11 or 12 injections?

**Dr. Pitcher:** In a typical case, I begin a treat-and-extend approach after the first three monthly injections. But, I try to take a patient-specific approach. Those with a small amount of fluid I may start with a single injection, whereas patients with a large hemorrhage will receive four initial injections. I usually treat and extend by 2-week intervals with a 12-week cap.

**Dr. Busbee:** I have used the treat-and-extend approach for quite some time. This was reinforced by the HARBOR data and the prn arm. Over the 2 years of the study, the average injection frequency was 9 to 10 weeks. I start my patients monthly. When they dry, I slowly extend them, knowing that the vast majority will begin to fail as we reach the 9- to 10-week mark. I prepare patients for that. If we can get that extra week, they have not failed therapy. Some patients just need drug all the time.

**Dr. Ehlers:** Another issue is complacency. I think we have all run into problems with it. For this reason, I make my prn patients see me every 4 to 5, occasionally 6 weeks, for 2 years after their last injection. It is a burden, but some people would really rather do that than be subjected to injections. If they can have two to three injections and never need it again, they say they would rather see me every month. This accounts for a small percentage of patients. If I do prn therapy, I think this regimented follow-up is critical. The only prn studies that have shown significant success in visual acuity required similar aggressive follow-up. It is a high-visit burden, but some patients prefer this approach.

**Dr. Ho:** Our patient, whose vision started at 20/50, has had three monthly injections of the drug of your choice. The patient has had some response and the subretinal fluid has dissipated. Visual acuity has stayed the same 20/50, and we are at month 4. The patient comes back with persistent thickening in the macula and cystic edema, indicating a partial response (Figure 3). What do you do next and what is your threshold for switching?

**Dr. Pitcher:** If there is a significant response, I stick to my initial therapy. If there is only a minimal response, I switch to a different drug, sometimes using the sampling programs. In the case of a total response, I extend with the initial therapy.

**Dr. Ho:** Do you rely on OCT imaging or visual acuity to determine a response?
Dr. Pitcher: I prefer using a combination of both, but I do lean more toward anatomic decision-making.

Dr. Busbee: I look for a partial anatomic response with the initial anti-VEGF at month 4. I know from the AMD trials that not every patient will have a great response in the first 3 months. I do not switch drugs quickly. At some point during the course of treatment, whether it is at 4 months or 6 months, I will alert patients to the existence of another drug and offer them a chance to try it. Very often patients will tell you they cannot detect any difference between drugs.

Dr. Ehlers: I like to get OCTs at every follow-up because I want to know the tempo of my patients’ fluid and whether they have been improving at every visit. In cases with ongoing improvement, I usually will not switch drugs; however, with continued persistence and no response in visual acuity, I will certainly think about switching. Another consideration that comes into play with switching is durability of response, not necessarily treatment response. In some patients on certain drugs I am unable to extend past 5 to 6 weeks, therefore I may switch therapies to assess for increased durability and the potential for increased interval. This is a different reason to switch than treatment failure.

Dr. Pitcher: I agree with Dr. Ehlers on this point. If I cannot extend someone past 6 weeks, then I will switch to a different drug.

Dr. Moshfeghi: I think that so many of us have come to rely upon this simple, refined noninvasive imaging test. The OCT provides useful, noninvasive, anatomic information. We are all overburdened. I will consider bringing a patient back in early to see if there is a response that might prove durable through week 4. OCT results might persuade you to switch, because patients see treatment durability as a serious issue."

—Allen C. Ho, MD

the initial loading injections suggested that those eyes may do better with aflibercept given every 4 weeks.

Dr. Moshfeghi: I think we differ about a very small period of time, a 4-week period rather than an 8- to 12-week period, where treat and extend occurs. You are decreasing patient burden by extending the patient out. I am decreasing the patient burden by performing fewer tests and increasing the efficiency of the office visit. Both approaches are interesting; however, we still evaluate the patient two or three times a year.

Dr. Ho: We have a lot of detailed information from outcomes in clinical trials in the first 52 weeks and in the first 96 weeks or 2 years, including longer-term trials with patients coming in at various intervals. I am candid with my patients about finding their best treatment cadence. I try to individualize the care. Regardless, patients are losing vision. The question is why are patients losing vision in the long run? Certainly, aging plays a role, whether it is cataracts or geographic atrophy (GA), independent of neovascular AMD. Why then are patients losing visual acuity gains achieved in the first 2 years of treatment, and what can we do about it?

Dr. Pitcher: I think there are multiple reasons. We know from the original HORIZON data that, without well-defined treatment criteria, patients lost vision. As we developed more refined criteria, as in the VIEW extension studies and the ASSESS study, patients maintained vision, but lost a few letters; however, not nearly as much as they did in the early HORIZON trial. I think what affects vision loss in the extension period are small recurrences. Even patients who are getting an injection every 4 weeks come in with new subretinal hemorrhages, despite ongoing treatment. It will be interesting to note if there is up-regulation of other proangiogenic cytokines in patients who are getting monthly injections of anti-VEGF. Can we prevent some of these small recurrences that are ultimately taking chunks of vision?

Dr. Ho: What other pathways might be affecting visual function over time?

Dr. Ehlers: There are likely several factors involved in loss of visual function over the long term. Lack of vigilance is one. We may try to push the envelope of follow-up interval. For any given recurrence, a patient might still go from 20/30 to 20/70 and never return to 20/30. This is my biggest concern with either the prn or the treat-and-extend approach.
**Dr. Busbee:** The problem appears to be undertreatment. When you go on a protocol-driven study, such as ASSESS, the common theme was that patients were given intensive therapy during the trial, and outcomes were positive. While this could be due to a drug switch in the study, it is equally plausible it is due to a change towards a more intensive treatment regimen once on protocol.

**Dr. Moshfeghi:** Apropos to the timeline of events, there is genetic susceptibility, inflammation, and drusen. If you eventually develop a CNV membrane, then you have vessel growth, leakage, fluid accumulation, and vision loss. When you are giving continuous anti-VEGF suppression, fluid may be coming and going during that period, but you are also taking care of other events that you may or may not be aware of and that OCT does not track. The patient’s 2-letter losses add up year after year. But this does not occur in patients who are receiving continuous therapy. If you give them 12 injections or you use a bimonthly dosing strategy, you are suppressing problems that we cannot track. This process might be helping you minimalize damage to the underlying retinal pigment epithelium and keep the photoreceptors healthier for a longer period of time.

**Dr. Ehlers:** RANGE is a treat-and-extend study. What impressed me most was that these patients had been receiving therapy for years while they were in the VIEW study. Even with the years of previous treatment, their average number of injections was approximately 7.9 in the RANGE study.

**Dr. Busbee:** We have enough data on AMD to know that most of these patients are going to fall into treatment somewhere between 6 and 8 weeks, with an occasional outlier. It is certain that you will have some failures.

**Dr. Ho:** Could the differences between real-world patients versus those who are willing to participate in a clinical trial account for the differences in visual acuity in wet AMD patients after 2 years of treatment in a clinical trial versus treatment in the real world, where intense surveillance may be lacking?

**Dr. Ehlers:** Even in the extension studies, patients tend to decline. There are two issues, the first one being that patients chosen for clinical trials tend to be healthier than those in the general population. They often do not have as many hospitalizations and other health issues that could interrupt their treatments. The second issue is that the research coordinators call the patients and keep them on track. In the real world, they might decide not to come in because they are seeing well. Patient characteristics and the overall treatment setting (clinical, research) definitely exert an effect on outcomes.

**Dr. Moshfeghi:** That is a really good point. My own patients tend to lose vision owing to extended hospitalizations during which they might have missed several months of injections. By the time they return to the office, early scarring will already have begun.

**Dr. Ho:** This can happen, of course, whether or not a patient is enrolled in a clinical trial. It is also true that patients enrolled in clinical trials tend to be healthier owing to exclusion criteria and selection bias. But if we are not getting the results achieved by the registration trials, we need to recognize that this process comes with a burden of treatment, which I define as the act of coming into the office. You might define it as coming to the office, plus the duration of time in the office, plus the testing. How do we then reconcile that undertreatment may be occurring across multiple large population database sets in this country and abroad?

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“Patient characteristics and the overall treatment setting… definitely exert an effect on outcomes.”

—Justis P. Ehlers, MD

**Dr. Moshfeghi:** I go back to the CATT data, where in year 2 some patients did not gain fluid. But then, fluid increased in the prn arms, and the only two groups that did not gain fluid were those in the monthly treatment arms. We have to bring a different mindset as to how we are going to treat these patients until we get a longer-duration drug or a combination drug.

**Dr. Ehlers:** One of the hopes for the future in AMD therapy is extending treatment intervals perhaps through combination therapies or with novel drug delivery systems. Many of these approaches are already in clinical trials.

**Dr. Moshfeghi:** Also, remember how difficult it was getting patients into the office for monthly injections? When we were able to offer patients bimonthly injections, more patients were on board. Now the new patients are put out by having to come in every other month. It is a matter of selling them on the efficacy of therapy.

**Dr. Busbee:** Apropos to undertreatment, it might be that we initially thought that treatment increased atrophy. When all the data were in, CATT and HARBOR dispelled this notion. Now, we feel better about treating people since the risk of atrophy with the drugs has been disproved. If a patient is going to get GA, there is not much we can do about it. At least we know the anti-VEGF is not responsible, but I am not sure how well known that point is across the country.

**Dr. Ho:** A port delivery system for ranibizumab is under investigation. This requires surgical implantation. There are also trials investigating stem cell and gene therapy. Genetically modified cells are implanted, which also requires surgery. Do you think these systems might help reduce the number of injections patients must receive? Do you think patients with wet AMD will be eager to undergo surgical events to save vision?
“It could take 5 years or more for us to develop a new treatment paradigm.”
—John D. Pitcher III, MD

Dr. Pitcher: I think patients will definitely be motivated. In recruiting for trials that require treatment-naïve patients, I have found that patients are not necessarily motivated to accept something new; however, when it comes to requiring injections every 4 weeks that might help, they become motivated. As for whether patients will tolerate surgical events, I do not think we have an answer to that yet. Necessity is the mother of invention. Perhaps within the next few years, some of these therapies will become clinic-based procedures.

Dr. Ho: Our capacity to evolve how we practice is remarkable. We went from being surgical specialists to seeing patients more often than their primary care doctors do. When we look back upon this era of injections, we might be able to say, ‘Remember when patients came in every 4 to 6 weeks?’ Nonetheless, there will still be an office burden to bear. Hopefully, a durable device will not only reduce the treatment burden, but will also increase efficacy for our patients.

Dr. Pitcher: In the last 10 years, there has been a revolution in our ability to impact blindness disease. Three of the four leading causes of blindness in America have been slowed down with anti-VEGF therapy: RVO, DME, and wet AMD. So many positive effects have emerged from anti-VEGF therapy, regardless of the medication you choose.

Dr. Ho: Where do you see us in 5 to 10 years for wet AMD? Are we going to be using different drugs? Are we going to be doing surgical implants?

Dr. Ehlers: I suspect in 5 years we will have a wider number of treatment choices that allow us to continue to optimize individualized therapy. I suspect we will not only have options for combination therapy, but we will also have new drug delivery system and potentially new interventional procedures.

Dr. Busbee: I always see the glass as half-full. In 5 years, I expect we will have very intriguing modes of treatment, different molecules, and new surgical interventions. That is why I participate in clinical trials. The other side is that we have been doing the same thing for 10 years. That tells you how high the bar is for developing something new. When I talk to my patients, I assure them we are really working hard to find something new, but first we have to bridge the gap. Because if we do not bridge it, they will not have vision, no matter what we have now.

Dr. Pitcher: It is important to let patients know what progress is being made, but it is also true that the bar has been set very high. It could take 5 years or more for us to develop a new treatment paradigm.

Dr. Moshfeghi: I agree with much that has been said here. I do not see us moving away from injecting any time soon. The frequency may decrease a bit as some new combinations enter the market, but I am not convinced they will impact the duration of therapy. I think the next real area of impact for us is the focus on drusen and preventing that divergence toward a choroidal neovascular membrane or GA. A stem cell or a retinal pigment epithelium might eventually become successful strategies for dry AMD. But I think the real key is to prevent patients from actually developing GA and choroidal neovascular membrane. This would be very interesting, but it will not occur in the immediate future.

Dr. Pitcher: We are fortunate to have any effect on major blinding eye diseases. As resources become more constrained, we need to do a better job in letting those who control these resources know how much our patients—whether they are 30-year-old diabetic patients or 75-year-old grandmothers—value their vision and seek to maintain it.

Dr. Ho: I think the future is bright because we are so active and because there are major investments in the diseases that we are working on for our patients. We are 10 years into a revolution-ary anti-VEGF therapy for wet AMD and I foresee new molecules including those that affect different pathobiologic pathways in our armamentarium in the next few years. The optimal use of anti-VEGF therapies for wet AMD requires greater understanding since unmet needs remain. We should consider the disconnect between how patients do in the first couple of years in clinical trials versus how they are doing in the real world in our practices. The take-home lessons are speculative, but one consensus from this group is that perhaps we are undertreating these patients. There are a variety of reasons for that—some we might not be able to surmount, such as the burden of treatment and days off required from work. This is something we need to remain mindful of while avoiding the vision creep or downward drift in making sure our patients receive the best treatment.

12. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular...
12 SUPPLEMENT TO RETINA TODAY JULY/AUGUST 2016

AMD in 2016: A Review of Treatment Guidelines and the Role of Early Appropriate Therapy

1. In the registration trials for AMD:
   a. 10% of patients gained less than 5 letters
   b. 20% of patients gained less than 5 letters
   c. 30% of patients gained less than 5 letters
   d. 40% of patients gained less than 5 letters

2. A 77-year-old woman, who is 20/30, has macular drusen and dry AMD, and a mild cataract in her left eye. She recently noticed new blurring of vision in her right eye. She has some hemorrhage, macular drusen, and thickening with subretinal fluid and intraretinal fluid on OCT. According to the panelists, what imaging tools are not preferred in this case?
   a. Fluorescein angiography
   b. Optical coherence tomography
   c. Ultrasonography
   d. Fundus autofluorescence

3. According to the panelists, OCT-A:
   a. Should not be used on advanced AMD patients
   b. Should only be used in cases of advanced AMD
   c. Could be used in the differential diagnosis of someone with drusen and subretinal fluid
   d. Might increase the potential of a better treat-and-extend outcome

4. The panelists noted ___________ is a common mimicker of wet AMD.
   a. Pigment epithelial defects
   b. Vitelliform lesions
   c. Polypoidal choroidal vasculopathy
   d. Cuticular drusen

5. Event rates for endophthalmitis between the anti-VEGF drugs:
   a. Are similar
   b. Favor bevacizumab over aflibercept
   c. Favor ranibizumab over aflibercept
   d. Favor aflibercept over either bevacizumab or ranibizumab

6. According to the panelists, follow-up studies are starting to show:
   a. About 5% of patients can go out longer than 12 weeks
   b. About 10% of patients can go out longer than 12 weeks
   c. About 15% of patients can go out longer than 12 weeks
   d. About 20% of patients can go out longer than 12 weeks

7. In MARINA, what percentage of patients gained 3 lines of vision after 12 consecutive months of treatment?
   a. 0%
   b. 5%
   c. 10%
   d. 15%

8. In HARBOR, the average injection frequency in the prn arm was:
   a. Every 4-5 weeks
   b. Every 5-6 weeks
   c. Every 7-8 weeks
   d. Every 9-10 weeks
### ACTIVITY EVALUATION

**Did the program meet the following educational objectives?**

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<tr>
<th>Objective</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
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<tbody>
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<td>Assess the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF therapies for common retinal diseases, including AMD</td>
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<td>Discuss the ocular and systemic effects of anti-VEGF therapies and how to educate patients on appropriate expectations</td>
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<td>Develop plans to initiate treatment for conditions such as AMD using anti-VEGF agents as well as better understand when to change therapeutic strategies</td>
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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
__________________________________________________________________________________
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If no, please identify the barriers to change.
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Please list any additional topics you would like to have covered in future Evolve Medical Education LLC CME activities or other suggestions or comments.
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