

Supplement to

March 2020

RT

Retina Today

INSIGHT INTO REAL-WORLD TREATMENT OF nAMD

A CME activity provided by Evolve Medical Education LLC.

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals.

Jorge Fortun, MD, Moderator

Mitul Mehta, MD

Hemang Pandya, MD

Veeral Sheth, MD

Distributed with

RT
Retina Today

Provided by


evolve
medical education

Insight into Real-World Treatment of nAMD

Release Date: March 2020
CME Expiration Date: March 2021

FACULTY



JORGE FORTUN, MD
MODERATOR

Bascom Palmer Eye Institute
Palm Beach Gardens, Florida



MITUL MEHTA, MD

University of California Irvine
Gavin Herbert Eye Institute
Irvine, California



HEMANG PANDYA, MD

Dallas Retina Center
Dallas, Texas



VEERAL SHETH, MD

University Retina & Macula Associates
University of Illinois
Chicago, Illinois

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a virtual roundtable discussion.

ACTIVITY DESCRIPTION

Retinal disorders, including age-related macular degeneration, diabetic eye disease, and retinal vein occlusion can result in vision loss if not treated early and continuously. Prevent Blindness America has found the total health care costs of vision problems in the United States in people older than 40 years to reach almost \$139 billion annually. Retina specialists must be continuously educated on the latest advances relating to the management of these diseases to allow for the best possible care for their patients.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and eye care professionals involved in the medical management of patients with retina disorders.

LEARNING OBJECTIVES

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

- **Identify** the current treatment options available for the management of common retinal diseases (neovascular age-related macular degeneration, diabetic eye disease, retinal vein occlusion).

- **Summarize** how treatment paradigms have evolved over time and how they relate to current treatment options.
- **Identify** the relationships between disease characteristics, drug, treatment frequency, visual and anatomic outcomes.
- **Implement** best practices using individualized patient treatment plans to ensure optimal outcomes for patients.
- **Recognize** the growing importance of imaging for use in disease management.

GRANTOR STATEMENT

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals.

ACCREDITATION STATEMENT

Evolve Medical Education LLC (Evolve) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Evolve designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

TO OBTAIN CREDIT

To obtain credit for this activity, you must read the activity in its entirety and complete the Pretest/Posttest/Activity

Evaluation/Satisfaction Measures Form, which consists of a series of multiple choice questions. To answer these questions online and receive real-time results, please visit <http://evolvemented.com/online-courses/1922-supp1>. Upon completing the activity and self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit*[™]. Alternatively, please complete the Posttest/Activity Evaluation/Satisfaction Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950.

DISCLOSURE POLICY

It is the policy of Evolve that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent conflict of interests relating to the topics of this educational activity. Evolve has full policies in place that will identify and resolve all conflicts of interest prior to this educational activity.

The following faculty/staff members have the following financial relationships with commercial interests:

Jorge Fortun, MD, and/or spouse, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Alcon/Novartis, Allergan, and Carl Zeiss Meditec. *Grant/Research Support*: Alcon/Novartis and Allergan.

Mitul Mehta, MD, and/or spouse, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant* and *Speaker's Bureau*: Novartis. *Stock/Shareholder*: Eyedaptic.

Hemang Pandya, MD, and/or spouse, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Speaker's Bureau*: Novartis.

Veeral Sheth, MD, and/or spouse, has had a financial agreement or affiliation during the past year with the following

commercial interests in the form of *Grant/Research Support*: Allergan, Alimera, Genentech, Novartis and Regeneron Pharmaceuticals. *Speaker's Bureau*: Alimera, Eyepoint, Genentech, and Novartis.

EDITORIAL SUPPORT DISCLOSURES

Erin K. Fletcher, MIT, director of compliance and education; Susan Gallagher-Pecha, director of client services and project management; and Cassandra Richards, director of education development, Evolve, have no financial relationships with commercial interests. Nisha Mukherjee, MD, peer reviewer, has no financial relationships with commercial interests.

OFF-LABEL STATEMENT

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Evolve, *Retina Today*, or Regeneron.

DIGITAL EDITION

To view the online version of the material, please visit <http://evolvemented.com/online-courses/1922-supp1>.



PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures Instructions for CME Credit.

1. Please rate your confidence in your ability to implement individualized patient treatment plans to ensure optimal outcomes for patients (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

2. At how many weeks did the EARLY analysis of DRCR Protocol I find an association with early response and long-term visual response?

- a. 4 weeks
- b. 12 weeks
- c. 20 weeks
- d. 36 weeks

3. Which of the following imaging modalities are appropriate for age-related macular degeneration (AMD) assessment?

- a. Optical coherence tomography (OCT)
- b. Fluorescein angiography
- c. Indocyanine green angiography
- d. OCT angiography
- e. All of the above

4. Which of the following are risk factors for macular atrophy development and progression?

- a. Subretinal fluid (SRF)
- b. Intraretinal fluid (IRF)
- c. Subretinal hemorrhage
- d. Long-term anti-VEGF therapy
- e. A, B, C
- f. B, C
- g. All of the above

5. An elderly patient with exudative AMD and fluctuating vision has remaining SRF after more than 20 injections of aflibercept and ranibizumab.

What is an acceptable treatment option?

- a. Keep treating with aflibercept
- b. Watch and wait
- c. Switch back to ranibizumab
- d. Switch to brolucizumab

6. A 75-year-old patient with neovascular AMD who has received anti-VEGF injections every 4 weeks for more than 1 year continues to have a small degree of persistent SRF and no IRF. The patient's visual acuity during the past 6 months has remained stable. Which of the following do you follow in your current clinical approach? Please select all that apply.

- a. Compare OCT today with prior OCTs to look for new IRF and SRF.
- b. Perform fluorescein angiography to evaluate for lesion activity.
- c. Keep treating at q4 week interval with the same anti-VEGF.
- d. Switch to another anti-VEGF treatment at q4 week interval.
- e. Gradually extend treatment to q8weeks if visual acuity remains stable and there is no increase in SRF and IRF.
- f. Consider PDT with or without steroids for treatment.

Insight into Real-World Treatment of nAMD

Caring for patients with neovascular age-related macular degeneration (nAMD) comprises a large part of our practices as retina specialists. The following discussion summarizes a meeting of experts in the field of retina in private practice and university settings. We discuss our individual approaches to diagnosis, disease management, and patient care based on clinical studies and unique experiences.

— Jorge Fortun, MD, Moderator

INITIATING THERAPY FOR AMD

Q | JORGE FORTUN, MD: Let's begin by discussing what you do for the patient whom you suspect has nAMD or has been referred to you by an outside provider with that potential diagnosis.

HEMANG PANDYA, MD: At baseline, whenever a patient is referred for nAMD, a full dilated exam and assessment of the peripheral retina is essential.¹ Given our high-quality imaging modalities, I obtain a baseline spectral-domain optical coherence tomography (SD-OCT). If the clinical picture is ambiguous, I feel a fluorescein angiography (FA) is an acceptable imaging option. I don't have OCT angiography (OCTA) in my clinic. I don't do Indocyanine green (ICG), for a few reasons: (1) I don't have access to a photodynamic therapy (PDT) laser, and (2) the quality of OCT has gotten so much better that we don't necessarily need ICG to diagnose.

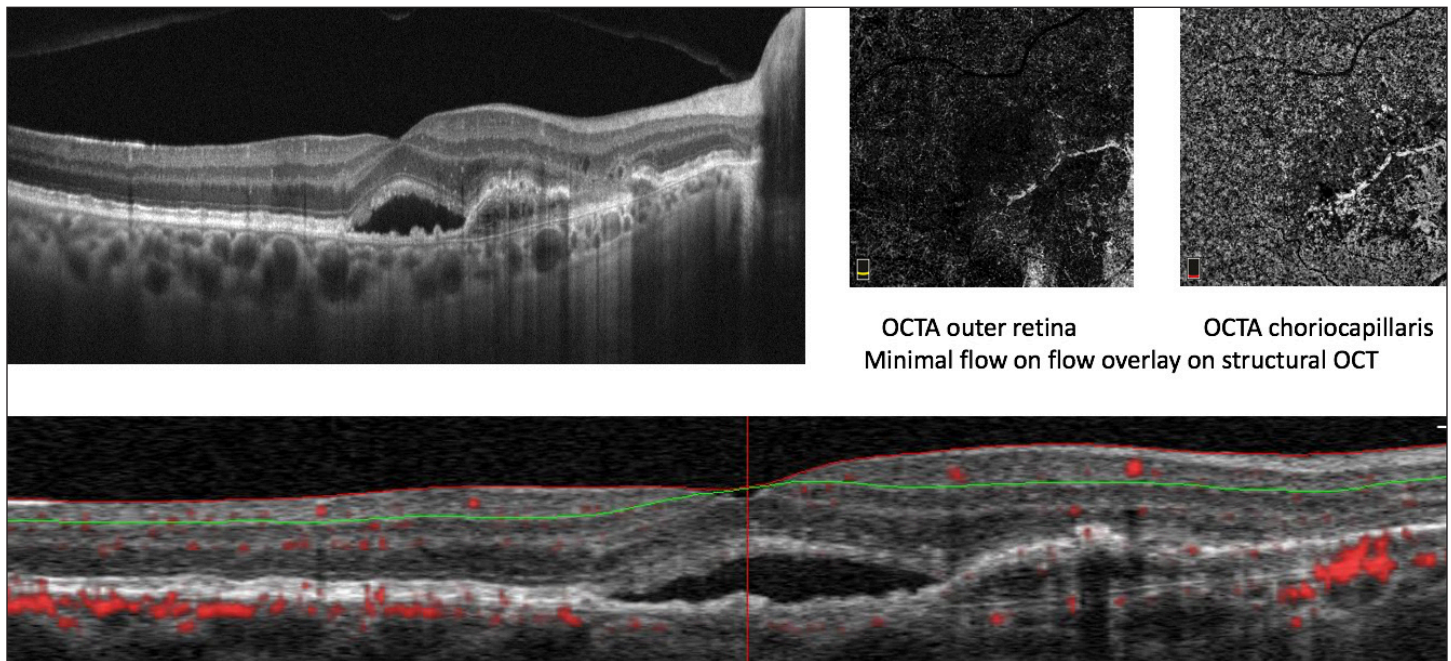
Q | DR. FORTUN: What do you believe is the role of OCTA, and do you have it in your practices? If so, how do you use it? Or do you see yourself obtaining the technology going forward?

MITUL MEHTA, MD: I do have OCTA in my clinics (Figure 1), and I use it pretty frequently. I like to get an OCT before I even see the patient, for the most part. Any patient who's been referred for AMD should get an OCTA. If it's dry or wet, it doesn't matter, because we notice in these patients, even if they're dry, that sometimes they will have a choroidal neovascular membrane that doesn't leak. So it's good to know that it was there before they leaked. It's when you know if they're starting to develop subretinal fluid (SRF) that it might be something else and you might be pointed one way or the other. Sometimes, especially in patients with polypoidal choroidal vasculopathy (PCV), I supplement the anti-VEGF treatment with the PDT laser, and if you're just looking at the things that light up on FA or ICG angiography, you might be treating areas that don't actually leak and don't need a PDT, which can have some side effects.

I do use OCTA in every patient who comes in needing an AMD diagnosis. Also, sometimes it can help differentiate between central serous retinopathy (CSR) and AMD because it's not always easy.²

VEERAL SHETH, MD: I am hearing some differences in how we all practice. I know Dr. Mehta and I have discussed this before. I love OCTA, and if we had this discussion a year ago, I probably would have given you a similar answer as Dr. Mehta. And what I'm finding now is I'm doing fewer and fewer OCTAs, especially during initial patient intakes. I do agree with the group in that I think you can catch these neovascular membranes that don't leak, but I find myself not treating those anyway because I wasn't seeing fluid on the standard OCT, and not a lot of leakage on the traditional FAs. I've actually cut down quite a bit on using OCTA because it's also time-consuming, and the imaging platform I have, the files take a lot of space. Therefore, just from a back-up and practical day-to-day data management standpoint, for me it wasn't worth the time and the data that it would take up to do OCTAs routinely. I perform an OCTA for cases in which I want an FA and the patient can't have an FA. I will use it as an alternative to traditional dye-based angiography, or if there's something going on and I want a little bit more information and I think it may help me lean one way or another when it comes to diagnosing or managing a patient.

Q | DR. FORTUN: I think these are all excellent points. In my own practice, OCTA has definitely begun to play a role, but that role is not quite clear yet. I think that role may be better defined in the future as we have clinical trial results that tell us what to do with that data. Also, as you know, the technology continues to improve, and the images become easier to interpret. The last point I'll make relates to one made previously; we've begun to identify these "type-zero CNVs," or subclinical CNVs³ where you have neovascular yet nonexudative CNVs, and that perhaps changes our follow-up on these patients. If we have a patient whom we think has neovascular complex, we may follow them more closely than we would have in the past. We would have previously diagnosed them with dry AMD and followed up at



Images courtesy of Caroline Baumal, MD

Figure 1. OCTA scan.

6 months or a year. Now that we've established what we do to evaluate these patients from a diagnostic imaging standpoint, what is your go-to anti-VEGF agent or do you have a default agent? If not, how do you determine with what agent to initiate therapy? Do you always use loading doses and then go to treat-and-extend? Do you have a fixed dosing interval? How do you decide what the treatment regimen will be?

DR. PANDYA: With regard to exudative AMD, bevacizumab is still my go-to treatment of choice. That being said, if a patient presents for a second opinion following treatment failure with bevacizumab, I will consider another anti-VEGF agent. Given that the CATT study⁴ showed equivalence between bevacizumab and ranibizumab, I start with bevacizumab. In terms of frequency of dosing, it really depends on the situation. Most often, I do start with monthly doses for the first few months, and then extend accordingly. In some patients who don't respond as well, I would possibly consider changing to aflibercept or brolucizumab.

DR. MEHTA: I generally start with bevacizumab because of price. A lot of insurance companies are requiring it for initial treatment, but one of the interesting things about my practice, because I'm at a university, I get a lot of second, third, and fourth opinions. Oftentimes, patients have had a previous dosing regimen, and usually we'll continue that if they say it's been effective. If they bring records, which rarely happens, we can then just continue them with what anti-VEGF they are already taking.

There are certain patients in whom I prefer to use certain treatments. For example, if a patient only has one eye, I typically will start with ranibizumab. The reasoning behind that is we have the longest dataset on ranibizumab. It's in prefilled syringes, and no

one has to draw up anything. In my opinion, it gives me a better sense of security about the side-effect risks, even though the rate of endophthalmitis is comparable among ranibizumab, aflibercept, and bevacizumab.⁵

I was practicing at the Veterans Affairs in Cincinnati when the first cases of bevacizumab endophthalmitis outbreaks happened there. UC Irvine provides care for the VA Clinic in Long Beach and we have a certain number of 100-mg vials of bevacizumab allotted per patient. So, it doesn't save the system as much money to give bevacizumab over ranibizumab, in that regard, because the VA believes that having compounded bevacizumab has a higher risk of endophthalmitis. I don't see that in my practice, but it certainly is what I am going to be a little more cautious about. But if they're in certain demographics, like South Korea, Japan, and certain parts of Asia, PCV is a bigger risk.⁶ Those with PCV tend to respond better to aflibercept⁷ so, if the patient seems more like that flavor of AMD, I may start with aflibercept.

DR. SHETH: I, too, generally begin patients on treatment with bevacizumab. However, we have had some difficulty during the past year obtaining bevacizumab. I think my pattern is similar to Dr. Mehta's in that I'll start with bevacizumab, but I might switch sooner than most people if after three or four injections I'm still seeing residual fluid. I may switch just because I like to extend these folks out, and if I'm having fluid with shorter intervals of bevacizumab injections, I'll switch to either aflibercept or ranibizumab, or more recently, brolucizumab.

When we had this shortage issue, I was starting patients with on-label medications because we were having issues where for weeks at a time, we weren't able to replenish the bevacizumab supplies. During that time, I was also noticing there were probably some

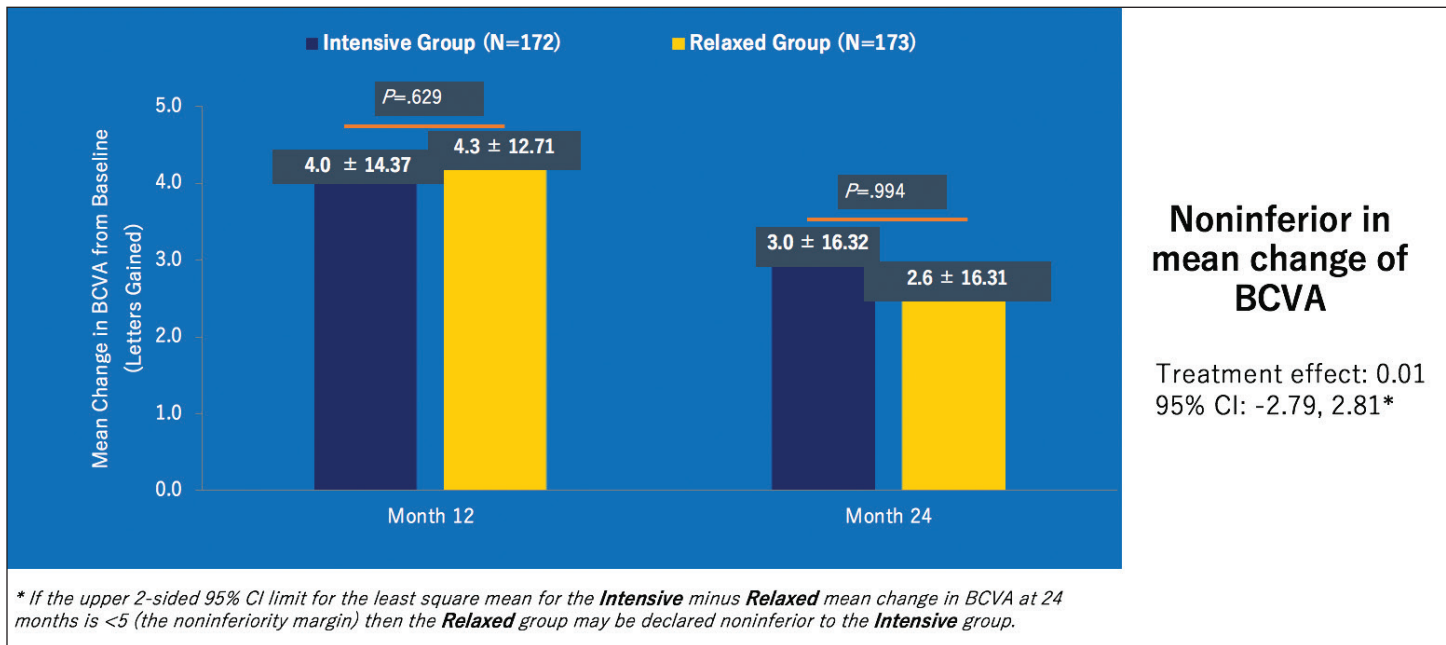


Figure 2. A small amount of SRF might be tolerable, and allowing some of that might be okay.

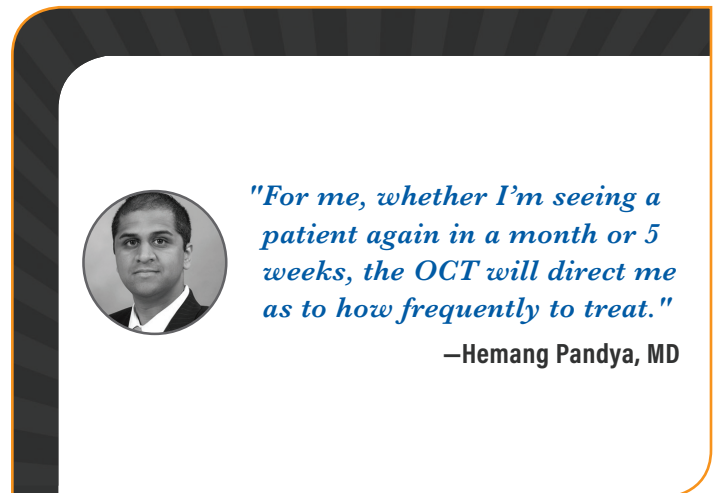
efficacy issues. When bevacizumab sits around in the fridge for a couple of weeks, you tend to see the efficacy decrease. Therefore, there are certain things I do worry about with bevacizumab. As Dr. Mehta said, there are sterility issues that could potentially happen. Because of some of these issues during the past year, I have been trending toward doing more of the on-label drugs when initiating therapy for AMD.

DR. MEHTA: I also am not a fan of a treat-and-extend regimen; I'm doing as needed (PRN) treatments, which we haven't really discussed yet.

TREATMENT RESPONSE

Q | DR. FORTUN: We'll discuss long-term treatment soon. Let's dive down a little deeper into how you gauge treatment response. What do you consider suboptimal treatment? At what point do you consider a switch? And if you are using bevacizumab, to what branded product do you switch? What has been the early experience with the newest agent that we have available to us, brolucizumab?

DR. PANDYA: In terms of early response, we base our treatment efficacies on visual acuity (VA) and OCT findings. But I do put a lot more emphasis on OCT than VA, given the lag time between OCT finding changes and VA. For me, whether I'm seeing a patient again in a month or 5 weeks, the OCT will direct me as to how frequently to treat. In terms of treatment failure and the need to change therapeutic agents, much of that is determined by how the patient feels. If a patient has had three treatments but tells me they aren't noticing any improvement, and the OCT shows persistent fluid, I will consider changing to another treatment. With regard to



brolucizumab, it seems promising but it's a little too early to make any definitive statements.

Q | DR. FORTUN: How much SRF are you willing to tolerate, as long as it's not worsening? Do you want the macula to be completely dry? And if you are completely dry, at what interval would you consider changing to another agent? So, in other words, to switch based not so much on anatomy, but on treatment burden? And obviously that should vary from patient to patient, but in general.

DR. SHETH: Regarding fluid and how much fluid I'm willing to tolerate, I'm becoming more tolerant of fluid. Some of the data, *(Continued on page 10)*

Case Discussion

By Mitul Mehta, MD, MS

This female patient presented in 2017 with a history of nAMD in both eyes. She had a typical past medical history of someone her age. Her anterior segment examination was essentially normal except for cataract surgery and slightly diminished vision. Her BCVA was 20/30 in her left eye and 20/40 in her right eye.

Her past medical history included hypertension, depression, early dementia, osteoporosis, arrhythmia, hyperlipidemia, lumpectomy for breast cancer (in remission, not on chemotherapy).

She had been receiving injections approximately every 8 weeks of aflibercept in each eye during the past 2 years on an

as-needed basis with fairly good preservation of vision in the left eye and mild decrease in the right eye.

Next steps for this would include imaging. In this chronically treated patient, OCT, FA and/or ICGA would be helpful. While fluorescein angiography (FA) is the gold standard for diagnosing neovascularization, an ICG can be helpful, especially in cases of polypoidal choroidopathy (PCV). SD-OCT has largely replaced FA and ICGA in the monitoring of chronic nAMD.¹⁻³

The terms “classic” and “occult” used to describe CNVM are angiographic terms, but these categories can often be determined by OCT. From a clinic flow standpoint, OCT is faster, less invasive, and easier to perform on all AMD patients than FA and does not require trained ophthalmic photographers to get an excellent image.¹⁻³

The patient’s OCT of the right eye (Figure 1), shows the presence of subretinal fluid, which indicates active leakage, and a fibrovascular PED, which indicates the presence of a type I or occult choroidal neovascular membrane (CNVM).

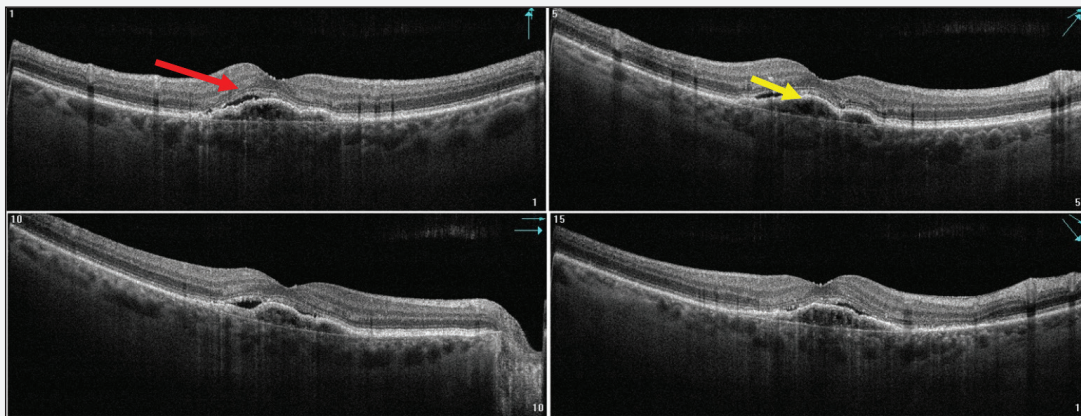


Figure 1. OCT image of the patient’s right eye. The red arrow points to subretinal fluid which indicates active leakage, and the yellow arrow points to a fibrovascular PED which indicates the presence of a type I or occult choroidal neovascular membrane (CNVM).

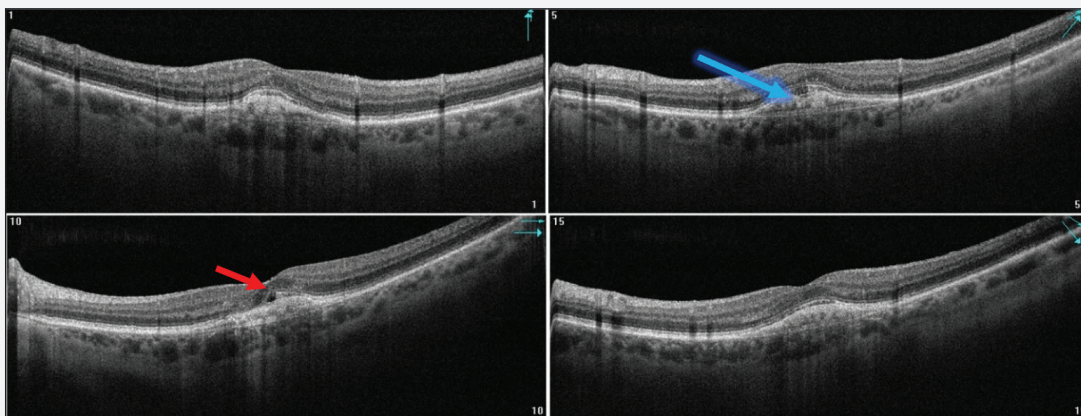


Figure 2. OCT image of the patient’s left eye. Notice the difference between the left and right eye. The red arrow again shows subretinal fluid, and the blue arrow shows a fibrovascular PED.

In the patient’s left eye (Figure 2), both subretinal fluid and fibrovascular PED are present, but this one has more hyperreflectivity, which implies more fibrous material in the subRPE space and less subRPE fluid.

Figure 3 is an OCTA scan that also shows CNVM in both eyes.

The ability to see them on OCTA means there is blood flow in the CNVMs. The right eye membrane is less well defined on OCTA, which is a limitation of OCTA to image occult membranes, which are slower flowing. However, the lack of leakage obscuring the details of the CNVM compared to FA can be an advantage as well.⁴⁻⁷

Despite the large well defined CNVM on OCTA of both eyes,

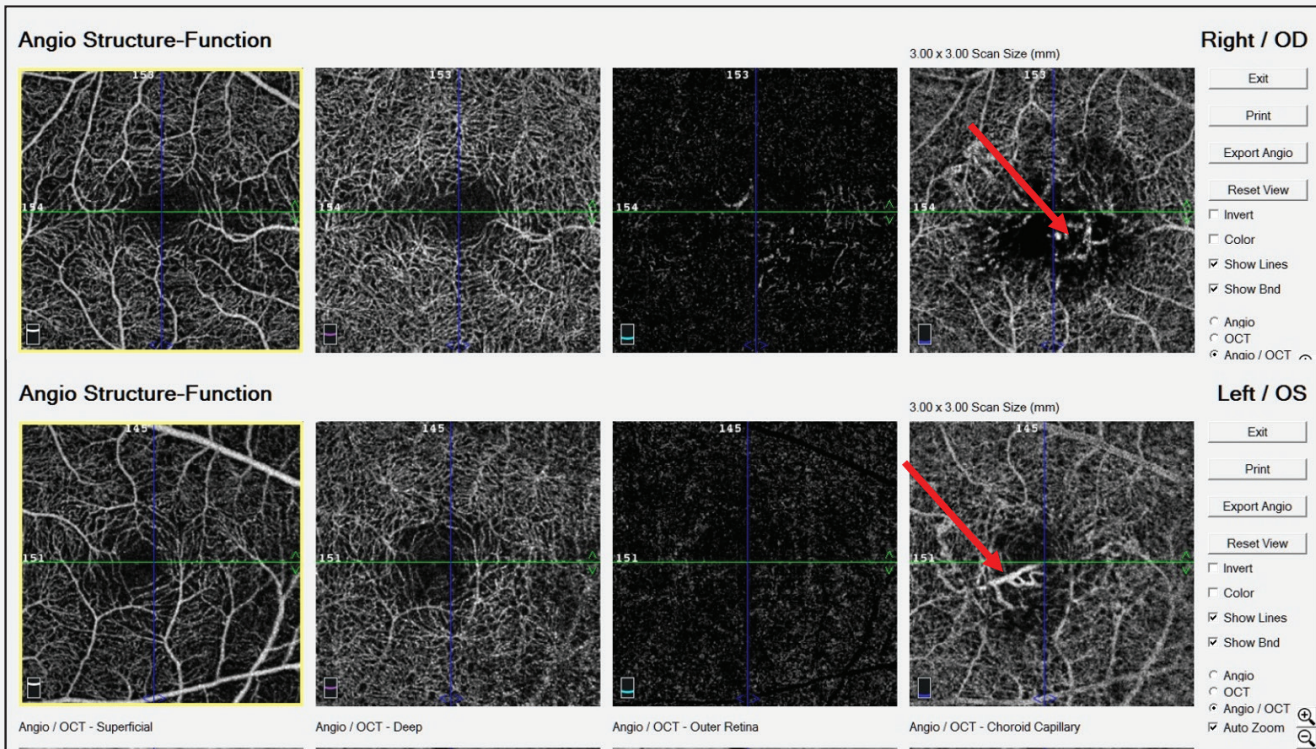


Figure 3. In this OCTA scan, the red arrows point to the CNVM in both eyes.

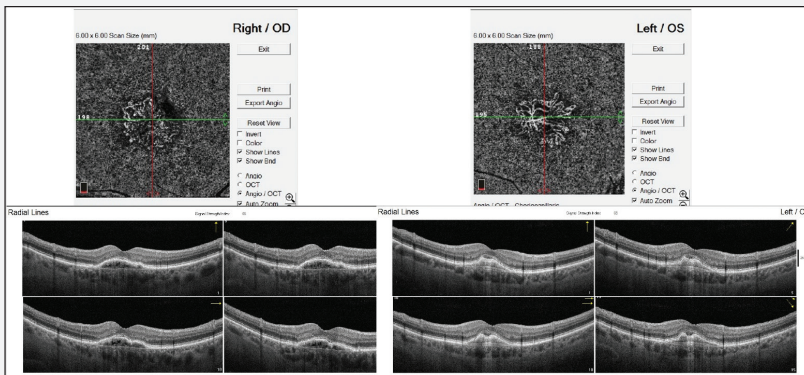


Figure 4. Despite the large well defined CNVM on OCTA of both eyes, there is no subretinal fluid in the right eye. In this case the BCVA in the right eye improved to 20/25 but dropped to 20/40 in the left eye.

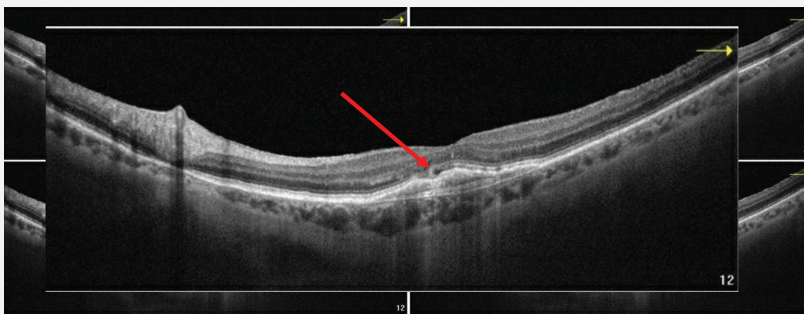


Figure 5. Look at all of the cuts. This OCT image shows a hint of SRF and the patient was symptomatic.

there is no subretinal fluid in the right eye (Figure 4). In this case the BCVA in the right eye improved to 20/25 but dropped to 20/40 in the left eye.

The take-home point for this case is to look at all of the cuts. There was a hint of subretinal fluid and the patient was symptomatic (Figure 5).

This patient has been receiving injections for 4 years. When she mentioned that her vision was not right, I accepted this as a good indicator there was disease activity. It is debatable if this is really subretinal fluid, but we treated her with aflibercept, and she called me 2 days later to say her vision was better.

1. Told R, Sacu S, Hecht A, et al. Comparison of SD-optical coherence tomography angiography and indocyanine green angiography in type 1 and 2 neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2018;59:2393-2400.
2. Arevalo JF, Lasave AF, Arias JD, et al. Clinical applications of optical coherence tomography in the posterior pole: the 2011 José Manuel Espino Lecture – Part II. *Clin Ophthalmol.* 2013;7:2181–2206.
3. Sharma S, Sayanagi K, Kaiser PK. Pathology detection rate of spectral domain optical coherence tomography devices. *Br J Ophthalmol.* 2014;98(Suppl 1):i3–i6.
4. de carlo TE, Romano A, Waheed NK, et al. A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreous.* 2015;1:5.
5. Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog Retin Eye Res.* 2016;50:1-24.
6. Miotto S, Zemella N, Gusson E, et al. Morphologic criteria of lesion activity in neovascular age-related macular degeneration: a consensus article. *J Ocul Pharmacol Ther.* 2018;34:298-308.
7. Schmidt-Erfurth U, Klimscha S, Waldstein SM, et al. A view of the current and future role of optical coherence tomography in the management of age-related macular degeneration. *Eye (Lond).* 2017;31:26–44.



"I will try to get the retina completely dry. However, if there is persistent SRF, and the patient's VA remains stable, I look at that SRF as a biomarker."

— Jorge Fortun, MD

(Continued from page 7)

including from the FLUID study⁸ (Figure 2) and others, demonstrate that a small amount of SRF might be okay, and allowing some of that might be okay from a vision standpoint and may allow you to extend the treatment interval for the benefit of the patient. So, in the real world, I have some patients in whom I can't get rid of every drop of SRF. I'm sure we all have these patients who we have brought in at 2 weeks to see if we could get rid of the fluid. And in the end, when you kind of back off and look at these patients, their vision really never fluctuates despite that there's some fluid. I think, over the course of time, I've become a little more tolerant of SRF.

Obviously, I think intraretinal fluid is different, and I really don't want to tolerate any intraretinal fluid (IRF), which ties into your question about interval and how far we are willing to stretch these patients' intervals. Based on those assumptions, with a small amount of SRF and no IRF, I like to extend treatment intervals to every 8 weeks (q8w), if possible. I think we're happy to get most patients to that range. It will be interesting to see with brodalumab what intervals we can reach, whether it's q8w or every 10 weeks (q10w) or every 12 weeks (q12w). But I think the trend for me on a treat-and-extend kind of protocol is to get to q8w. And if we can't, that's when we consider switching patients.

DR. MEHTA: I agree with that 100%. One thing about leaving fluid for 8 weeks, which I think goes back to the original aflibercept data, is that it really doesn't seem to affect patients' vision. I have patients whom I have never been able to get them dry. Not even 1 week, 2 weeks, 4 weeks after an injection, on every medication. I've tried all of them, and they still have SRF. And 4 years later, they're still 20/20 with SRF.

There is one patient in particular whom I saw recently for follow-up. She noticed her vision become worse at 5 weeks, so she now has to return at 4 weeks. If I'm on vacation, one of my partners will deliver her injection. Some patients are just very, very particular about noticing changes and some are not. You have to gauge the patient and when they have symptoms and determine if you're going to leave fluid behind in the subretinal space.

I agree completely with Dr. Sheth in that I don't like IRF. What

I am seeing is that some of these patients with IRF do not entirely respond to anti-VEGF agents, likely caused by an inflammatory component.⁹ I'll sometimes add a steroid and that will clear the IRF when the anti-VEGF agents do not. I know that isn't based on any literature, but that is my experience.

DR. FORTUN: These are all great points. I'll add and echo what some of you have said. Clinical trial data has shown that SRF can be looked at more as a biomarker.¹⁰ Even though we are for the most part OCT-guided in how we administer treatment, we don't necessarily need a completely dry macula from an SRF standpoint. IRF certainly represents a different sort of animal all together.

I will try to get the retina completely dry. However, if there is persistent SRF, and the patient's VA remains stable, I look at that SRF as a biomarker. I consider that small amount of SRF to be that patient's optimum treatment at baseline, and in the absence of any change in VA, what it probably means is that I've gotten that CNV to sort of a steady state. There is some evidence from the CATT data⁴ and some other trials¹¹ to suggest that perhaps over-inhibition of these CNVs could lead us down the pathway of advanced nonexudative macular degeneration by ridding ourselves of this potentially protective CNV and leading us toward geographic atrophy (GA). I think that we're starting to change the way we look at SRF and realize that all fluid is not created equal.

LONG-TERM AMD MANAGEMENT

Q | DR. FORTUN: Let's talk about long-term management of AMD. Once you've got a patient established into an interval, how do you manage this patient going forward from a practical logistics standpoint? How often are you imaging this patient? Are you doing injection-only visits?

DR. SHETH: I want to talk about what I categorize as the medical management of these patients versus the social management of these patients. I think they both warrant a conversation.

Medically speaking, once we know the treatment interval, we will simply bring them in for OCT and injection visits; we don't perform a full examination for a lot of these patients. Certainly, at some

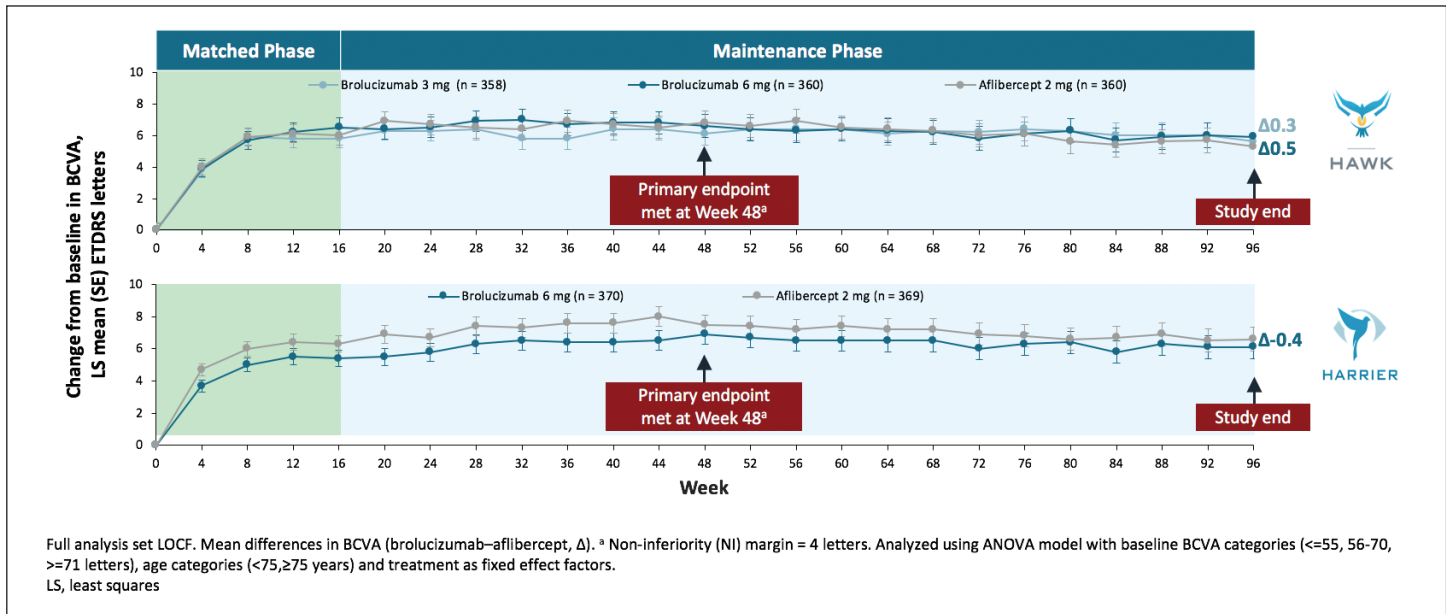


Figure 3. HAWK / HARRIER: BCVA change, baseline to 96 weeks.

interval, around every 3 months or so, we will perform a full exam to make sure we're not missing anything. We will check the state of the lens and things like that.

The social side of it is also a little tricky sometimes, I think. A lot of these patients you've been treating for years, and they wonder when it's going to end, or must it keep going indefinitely. I am curious to see what others have to say on this and how you're managing some of these conversations. How are you managing the expectations for the patients, but also how do you give these patients hope? What's your message to these patients in the long run?

DR. MEHTA: I agree with Dr. Sheth. I examine the patient every time, unless they're a bilateral patient who doesn't want to have same-day bilateral injections. For those patients who come in for the second eye injection, I don't examine them, I just do the injection. But, otherwise, I examine patients every time. And a lot of that's driven by the fact that I'm at a teaching institution, and I have fellows and residents with me, and I want them to practice examining patients. We talk about different things each time. Do I really need to? No. And in fellowship we didn't, actually. We would just do the series of three injections. Once the interval was decided, it was set in stone pretty much at that point. There's no real reason that you have to examine the patient every single time. Very basic things: vision, pressure, dilation, and OCT if necessary. VA and intraocular pressure (IOP) are the main things we look at for these patients. The important point here is that I do examine the patient every time.

DR. FORTUN: I also want to comment about the science of medicine and the art of medicine, which refers to the social aspects of patient care. If you look at real-world data, such as the recent study from David Williams and colleagues that looked at this metadata,

looking at almost 50,000 eyes that showed an overall undertreatment of patients.¹² If you look at the few patients at the SEVEN-UP study,¹³ an observational extension study of MARINA, ANCHOR, and HORIZON, in which there was an average loss in vision from what was shown in the clinical trial data, I think that speaks to the treatment burden and the social aspect of treating patients in the real world, whether it has to do with transportation or comorbidities, because many of our patients are elderly patients. In the long term, that perhaps leads to real-world results that are substantially inferior to some of the results seen in clinical trials. I think that's an important consideration to keep in mind.

Talking about treatment frequency and treatment algorithms, let us discuss the data that supports or refutes different treatment strategies. Do we choose to treat as true PRN? Do we implement a treat-and-extend regimen? Or do we consider fixed dosing intervals, whether that be monthly or something else. With brolucizumab, based on data from HAWK and HARRIER,¹⁴ we could offer quarterly dosing. There are some quarterly dosing data for ranibizumab, too.^{15,16} What treatment strategy do you all choose, and what evidence do you use to back that up?

DR. PANDYA: In terms of treatment frequency, many studies have shown that the more frequent the injection, especially during the first year of treatment, the less likely the burden in subsequent years. I know the CATT trial⁴ showed that monthly ranibizumab was optimal for OCT changes. IVAN,¹⁷ conducted outside the United States, also showed that. But when you look at the VIEW trial¹⁸ with aflibercept, for example, it showed that every 2-month dosing (q2month) was nearly equivalent to monthly ranibizumab.

With HAWK and HARRIER¹⁴ the results indicate that patients can be extended out to almost 3 months as well (Figure 3). So, the studies have all shown that at various time points medications either

have higher efficacy and can be extended longer, or maybe a lower efficacy and must be used more frequently. A lot of it is dependent upon the patient's particular condition, as well as how they present and respond to treatment. I feel that there is a component of pharmacogenomics that we don't fully understand. But in general, I feel an initial dosing of monthly or q5w followed by extended treatment is ideal. I feel that PRN can get a little tricky when it comes to AMD patients, especially given its chronic and recurrent nature.

DR. MEHTA: I actually do PRN treatment for nAMD, and the reason is almost entirely because of the social aspect we discussed earlier. There are some people who don't respond well, and there are some who respond incredibly well. I don't give loading doses; I just give them one injection and see the response. And I have some patients who do not need a second injection for 7 months. Later on, patients sometimes develop a need for more frequent injections. At that point, I bring them back monthly and then eventually space out the injections.

If the patient comes in 4 weeks later and they don't have any fluid, and there's no real concerning signs or enlargement of their PEDs or things like that, then I'll bring him or her back in another 4 weeks. I'll just extend them right away, because it's like I've already done the treat-and-extend regimen because I treated them the first time. For me it seems like PRN works well.

I do become a little hesitant around 3 to 4 months, because that's when aflibercept, ranibizumab, and bevacizumab are mostly out of the system; we don't know about brolucizumab yet. That's when I usually become more concerned, so I may add another injection at the 3-month mark, especially if the patient is traveling or has some other social reason for me to give him or her a "prophylactic" quarterly injection. But for the most part, I do PRN for nearly all my AMD patients.

DR. SHETH: I think PRN treatment is a different conversation that you have with your patients compared with a treat-and-extend regimen. With treat-and-extend, the patient knows exactly what's going to happen at that visit. Their only real question is when their next visit will be. For me, I think one of the reasons I like treat-and-extend is because it removes that conversation from visit to visit. Therefore, I simply tell them when they are returning for their injection and then we review the OCT together. However, I agree with you, Dr. Mehta. I think you have to figure out how to make it fit. I think a lot of it is based on your patient population and whether you're teaching residents. For a private practice setting, a lot of it is really more about operationally streamlining everything as much as possible. And I think that might be why there's a difference in how we practice.

DR. FORTUN: To recap our discussion on the management of nAMD, it seems that we all use OCT as our diagnostic and treatment-monitoring tool. The takeaway is that this is not a one-size-fits-all disease. Everything from drug choice to treatment strategy needs to be customized to the individual patient's disease and social situation. You can look at all the trials and they show us that undertreatment, whatever that may represent, whether it's persistent fluid or decreasing vision, leads to a poorer outcome.¹⁹ Even if you look at the treat-and-extend trials^{20,21} or some of the quarterly dosing trials and subgroup analyses,^{15,16} there are patients who did well. I think the good news for us as retina specialists is that we have a sturdy armamentarium of pharmacotherapeutic agents that we can use in our patients, and we just need to customize the regimen to each patient's individual disease and situation. Thank you, everyone, for this engaging discussion. ■

1. Mayo Clinic. Wet macular degeneration. <https://www.mayoclinic.org/diseases-conditions/wet-macular-degeneration/diagnosis-treatment/drc-20351113>. Accessed February 28, 2020.
2. Perrott-Reynolds R, Cann R, Cronbach N, et al. The diagnostic accuracy of OCT angiography in naive and treated neovascular age-related macular degeneration: a review. *Eye (Lond)*. 2019;33(2):274-282.
3. Heiferman MJ, Fawzi AA. Progression of subclinical choroidal neovascularization in age-related macular degeneration. *PLoS ONE* 14(6): e0217805.
4. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897-1908.
5. Rayess N, Rahimy E, Storey P, et al. Postinjection endophthalmitis rates and characteristics following intravitreal bevacizumab, ranibizumab, and aflibercept. *Am J Ophthalmol*. 2016;165:88-93.
6. Honda S, Matsumiya W, Negi A. Polypoidal choroidal vasculopathy: clinical features and genetic predisposition. *Ophthalmologica*. 2014;231:59-74.
7. Kawashima Y, Oishi A, Tsujikawa A, et al. Effects of aflibercept for ranibizumab-resistant neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2015;253:1471.
8. Guymer RH, Markey CM, McAllister IL, et al; FLUID Investigators. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723-734.
9. Zhang X, Lai TTY. Baseline predictors of visual acuity outcome in patients with wet age-related macular degeneration. *Biomed Res Int*. 2018; 2018: 9640131.
10. Nisarog P, Joshi NP, Adam NK, et al. Optical density of subretinal fluid as a predictive biomarker for eyes with chronic central serous retinopathy treated with eplerenone. *J VitreoRetin Dis*. 2018;2(1):6-11.
11. Holekamp NM et al. HARBOR Post Hoc Analysis. Presentation at the 42nd Macula Society Annual Meeting; Bonita Springs, FL, USA, February 13-16, 2019.
12. Dalton M. How AMD patients are treated in the 'real world.' *Modern Retina*. <https://www.modernretina.com/asrs/how-amd-patients-are-treated-real-world>. Updated July 22, 2018. Accessed February 11, 2020.
13. Bhisitkul RB, Desai SJ, Boyer DS, et al. Fellow Eye comparisons for 7-year outcomes in ranibizumab-treated AMD subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP Study). *Ophthalmology*. 2016;123(6):1269-1277.
14. Duigel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84.
15. Eichenbaum DA, et al. Quarterly anti-VEGF dosing for the treatment of neovascular age-related macular degeneration: a cross-trial comparison. Presented at: Association for Research in Vision and Ophthalmology annual meeting; April 28-May 3, 2018; Honolulu.
16. Schlingemann RO, Schmidt-Erfurth U, Eldem B, et al. Safety and efficacy of quarterly vs. monthly ranibizumab injections in patients with neovascular age-related macular degeneration: 12-months results of the EXCITE study. *Invest Ophthalmol Vis Sci*. 2009;50:2382.
17. IVAN Study Investigators: Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119(7):1399-411.
18. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
19. Monés J, Singh RP, Bandello F, et al. Undertreatment of neovascular age-related macular degeneration after 10 years of anti-vascular endothelial growth factor therapy in the real world: the need for a change of mindset. *Ophthalmologica*. 2020;243:1-8.
20. Wykoff CC, Ou WC, Brown DM, et al. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration 2-year results of the TREX-AMD study. *Ophthalmology Retina*. 2017;1:314-321.
21. Ohji M, Okada AA, Takahashi K, et al. Two different treat and extend dosing regimens of intravitreal aflibercept for wAMD in Japanese patients: 52 week results of the ALTAIR Study. Presented at: Euretina Congress; September 7-10, 2017; Barcelona.

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please visit <https://evolvemeded.com/online-courses/1922-supp1>. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____ MD/DO participant OD non-MD participant

Phone (required) _____ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession	Years in Practice	Patients Seen Per Week (with the disease targeted in this educational activity)	Region	Setting	Models of Care
<input type="checkbox"/> MD/DO	<input type="checkbox"/> > 20	<input type="checkbox"/> 0	<input type="checkbox"/> Northeast	<input type="checkbox"/> Solo Practice	<input type="checkbox"/> Fee for Service
<input type="checkbox"/> OD	<input type="checkbox"/> 11-20	<input type="checkbox"/> 1-15	<input type="checkbox"/> Northwest	<input type="checkbox"/> Community Hospital	<input type="checkbox"/> ACO
<input type="checkbox"/> NP	<input type="checkbox"/> 6-10	<input type="checkbox"/> 16-30	<input type="checkbox"/> Midwest	<input type="checkbox"/> Government or VA	<input type="checkbox"/> Patient-Centered Medical Home
<input type="checkbox"/> Nurse/APN	<input type="checkbox"/> 1-5	<input type="checkbox"/> 31-50	<input type="checkbox"/> Southeast	<input type="checkbox"/> Group Practice	<input type="checkbox"/> Capitation
<input type="checkbox"/> PA	<input type="checkbox"/> <1	<input type="checkbox"/> 50+	<input type="checkbox"/> Southwest	<input type="checkbox"/> Other	<input type="checkbox"/> Bundled Payments
<input type="checkbox"/> Other				<input type="checkbox"/> I do not actively practice	<input type="checkbox"/> Other

LEARNING OBJECTIVES**DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?****AGREE****NEUTRAL****DISAGREE**

Identify the current treatment options available for the management of common retinal diseases (neovascular age-related macular degeneration, diabetic eye disease, retinal vein occlusion).

Summarize how treatment paradigms have evolved over time and how they relate to current treatment options.

Identify the relationships between disease characteristics, drug, treatment frequency, visual and anatomic outcomes.

Implement best practices using individualized patient treatment plans to ensure optimal outcomes for patients.

Recognize the growing importance of imaging for use in disease management.

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to implement individualized patient treatment plans to ensure optimal outcomes for patients (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

2. At how many weeks did the EARLY analysis of DRCR Protocol I find an association with early response and long-term visual response?

- a. 4 weeks
- b. 12 weeks
- c. 20 weeks
- d. 36 weeks

3. Which of the following imaging modalities are appropriate for age-related macular degeneration assessment?

- a. Optical coherence tomography (OCT)
- b. Fluorescein angiography
- c. Indocyanine green angiography
- d. OCT angiography
- e. All of the above

4. Which of the following are risk factors for macular atrophy development and progression?

- a. Subretinal fluid (SRF)
- b. Intraretinal fluid (IRF)
- c. Subretinal hemorrhage
- d. Long-term anti-VEGF therapy
- e. A, B, C
- f. B, C
- g. All of the above

5. An elderly patient with exudative AMD and fluctuating vision has remaining SRF after more than 20 injections of aflibercept and ranibizumab. What is an acceptable treatment option?

- a. Keep treating with aflibercept
- b. Watch and wait
- c. Switch back to ranibizumab
- d. Switch to brolucizumab

6. A 75-year-old patient with neovascular age-related macular degeneration who has received anti-VEGF injections every 4 weeks for more than 1 year continues to have a small degree of persistent SRF and no IRF. The patient's visual acuity during the past 6 months has remained stable. Which of the following do you follow in your current clinical approach? Please select all that apply.

- a. Compare OCT today with prior OCTs to look for new IRF and SRF.
- b. Perform fluorescein angiography to evaluate for lesion activity.
- c. Keep treating at q4 week interval with the same anti-VEGF.
- d. Switch to another anti-VEGF treatment at q4 week interval.
- e. Gradually extend treatment to q8weeks if visual acuity remains stable and there is no increase in SRF and IRF.
- f. Consider PDT with or without steroids for treatment.

ACTIVITY EVALUATION

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.

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 _____

This activity improved my competence in managing patients with this disease/condition/symptom. ___ Yes ___ No

Probability of changing practice behavior based on this activity: ___ High ___ Low ___ No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ___

Change in nonpharmaceutical therapy ___

Change in diagnostic testing ___

Choice of treatment/management approach ___

Change in current practice for referral ___

Change in differential diagnosis ___

My practice has been reinforced ___

I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

___ Cost

___ Lack of opportunity (patients)

Other. Please specify: _____

___ Lack of consensus or professional guidelines

___ Reimbursement/insurance issues

___ Lack of administrative support

___ Lack of resources (equipment)

___ Lack of experience

___ Patient compliance issues

___ Lack of time to assess/counsel patients

___ No barriers

The design of the program was effective for the content conveyed.

___ Yes ___ No

The content was relative to your practice.

___ Yes ___ No

The content supported the identified learning objectives.

___ Yes ___ No

The faculty was effective.

___ Yes ___ No

The content was free of commercial bias.

___ 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

___ Medical Knowledge

___ Practice-Based Learning and Improvement

___ Interpersonal and Communication Skills

___ Professionalism

___ System-Based Practice

Additional comments:

___ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

