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Elevating nAMD Management Through Advances in Durability

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Content Source

This continuing medical education (CME) activity captures content from a live-virtual symposium.

Activity Description

This supplement summarizes a discussion on fluid biomarkers and their association with long-term visual outcomes for patients with neovascular age-related macular degeneration. The faculty debate key clinical trial data/post hoc analyses in addition to real-world experience.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Describe** the current treatments available to treat neovascular age-related macular degeneration (nAMD)
- **Discuss** the considerations involved in the choice of anti-VEGF agent and tailoring treatment regimens for individual patients
- **Evaluate** clinical evidence for biomarkers that are prognostic of optimal visual outcomes
- **Summarize** the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in nAMD

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PRETEST QUESTIONS

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1. Please rate your confidence in your ability to summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in neovascular age-related macular degeneration (nAMD) (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. According to the PULSAR trial, which of the following statements is TRUE?

A. Aflibercept 8 mg dosed every 12 or 16 weeks was inferior to aflibercept 2 mg dosed every 8 weeks
B. Aflibercept 8 mg dosed every 12 or 16 weeks was superior to aflibercept 2 mg dosed every 8 weeks
C. Aflibercept 8 mg dosed every 12 or 16 weeks was noninferior to aflibercept 2 mg dosed every 8 weeks
D. Aflibercept 8 mg dosed every 12 or 16 weeks was equivalent to ranibizumab dosed every 8 weeks

3. A 64-year-old man presents to your clinic with a chief complaint of visual distortion. On examination you note 20/50 VA in his right eye. Fundus examination reveals thickening in the macula. OCT angiography shows a drusenoid pigment epithelial detachment (PED) with adjacent subretinal fluid. You decide to inject him with monthly ranibizumab, but the size of his PED continues to increase, along with increasing cystic intraretinal fluid. All of the following are reasonable next steps in management of this patient EXCEPT:

A. Switch to intravitreal aflibercept 2 mg
B. Switch to faricimab
C. Switch to intravitreal aflibercept 8 mg
D. Maintain on monthly ranibizumab

4. You are evaluating a 72-year-old woman with nAMD. She is currently receiving intravitreal aflibercept 2 mg and is on a treat-and-extend protocol. Her last injection was 6 weeks prior. On examination, you note a new macular hemorrhage and increased cystic intraretinal fluid on her OCT compared to her prior imaging. She was previously maintained well on monthly aflibercept. Which of the following is the next best step in management of this patient?

A. Extend treatment interval by 2 weeks
B. Extend treatment interval by 4 weeks
C. Shorten treatment interval by 2 weeks
D. Shorten treatment interval by 4 weeks

5. Which of the following retinal fluid types has the most negative impact on visual acuity?

A. Persistent intraretinal fluid
B. Persistent subretinal fluid
C. Subretinal pigment epithelial fluid
D. Nonpersistent subretinal fluid

6. You are managing a 74-year-old patient with nonexudative AMD. You note subtle changes on OCT in her retinal anatomy and are concerned that she is developing exudative AMD. Due to a fluorescein shortage, you cannot obtain a fluorescein angiogram. What is the next best step?

A. Obtain fundus autofluorescence
B. Obtain OCT angiography
C. Obtain B-scan ultrasound
D. Obtain fundus photography

Elevating Neovascular Age-Related Macular Degeneration Management Through Advances in Durability

The current treatment armamentarium for neovascular AMD (nAMD) includes off-label bevacizumab, on-label ranibizumab, and on-label aflibercept 2 mg. We consider these first-generation therapies and use them routinely in clinical practice. We may be less familiar with second-generation therapies, such as brolucizumab, the Port Delivery System (PDS; currently on recall), faricimab, and aflibercept 8 mg, so-called because they attempt to extend the success we have seen with first-generation agents.[1-9] We are fortunate to practice at a time when we have multiple options for our patients. Herein, we consider clinical trial and real-world experience with these second-generation agents.

— Diana V. Do, MD, Program Chair

BREAKING GROUND: AN EXPLORATION OF SECOND-GENERATION THERAPIES

Aflibercept 8 mg

Diana V. Do, MD

Aflibercept 8 mg was the most recent agent (August 2023) to receive US FDA approval for the treatment of nAMD. The impetus to develop this therapy was the idea that increasing the molar dose, in this case by four-fold, could improve vitreal retention, thereby possibly providing added visual, anatomic, and/or durability benefits that would decrease the treatment burden. We have previously seen examples where increasing the molar dose of an anti-VEGF agent resulted in some clinical benefit.[10,11] In the animal studies, aflibercept 8 mg demonstrated a three-fold increase in half-life within the eye compared to aflibercept 2 mg.

Following the phase 2 CANDELA trial in patients with nAMD that showed no new safety signals and an indication that aflibercept 8 mg had potential for added therapeutic benefit,[12] a global phase 3 trial, PULSAR, enrolled more than 1,000 treatment-naïve patients with nAMD. Aflibercept 8 mg, given every 12 or 16 weeks was compared to standard aflibercept 2 mg given every 8 weeks.[8] The study met its primary endpoint of noninferiority in vision gains from baseline to week 48. Whether dosed every 12 or 16 weeks, aflibercept 8 mg resulted in very rapid and robust visual acuity gains after three initial monthly injections. This was noninferior to aflibercept 2 mg. Even in terms of anatomic change, aflibercept 8 mg resulted in rapid reductions in central retinal thickness (CRT), which were sustained through 1 year of treatment.

More importantly, during the first year of treatment, 79% and 77% of eyes randomized to aflibercept 8 mg every 12 or 16 weeks, respectively, were able to maintain this dosing interval. Overall, when both aflibercept 8 mg groups were pooled, 83% of eyes achieved dosing intervals of 12 weeks or greater.[8] Notably, in the first 48 weeks of the study, patients in the aflibercept 2 mg group received an average of 6.9 injections, compared to 6.1 and 5.2 injections in the aflibercept 8 mg 12-week and 16-week groups, respectively.

Recent 2-year data from this trial showed that 88% of all eyes that received aflibercept 8 mg were on a 12-week or greater dosing interval by the end of 2 years of treatment.[9] In fact, 78% of all eyes receiving aflibercept 8 mg maintained at least a 12-week dosing interval throughout the 2-year period. During year 2 of the study, eyes were allowed to extend beyond the intervals assigned in year 1. As such, 71% of eyes randomized to aflibercept 8 mg were dosed at intervals of 16 weeks or longer, including 47% of eyes that met the extension criteria for 20-week dosing or greater, and 28% of eyes that achieved 24-week intervals.[9]

We always stress that safety is very important for any new treatment. The safety data from the thousands of patients that were enrolled in the aflibercept 8 mg trials showed that the safety of this higher dose was comparable to that of aflibercept 2 mg, with very low rates of intraocular inflammation (IOI) and no cases of retinal vasculitis or occlusive vasculitis. This initial safety report looks very promising.

Faricimab

Adrienne W. Scott, MD, FASRS

The TENAYA and LUCERNE trials were the two phase 3 trials evaluating the safety and efficacy of faricimab for the treatment of nAMD, compared to aflibercept 2 mg.[6,7] More than 1,300 patients with treatment-naïve nAMD were randomized to faricimab or aflibercept arms. The faricimab dosing arm included four monthly loading doses, followed by disease activity assessments at weeks 20 and 24. This was an interesting aspect of the study—the investigator could extend the treatment arm in the faricimab group, if disease activity was judged to be stable at weeks 20 and 24.[7] Therefore, patients that demonstrated disease activity at week 20 or 24 received 8-weekly or 12-weekly injections, respectively, while others received injections every 16 weeks. The primary endpoint of noninferiority in mean change in BCVA from baseline, averaged over the 40-, 44-, and 48-week visits, was met.[6]

Over 2 years, faricimab dosed up to q16w had noninferior vision gains and comparable reductions in central subfield thickness (CST) to aflibercept 2 mg.[13] Both demonstrated dramatic improvements in visual acuity and CST, which were maintained throughout the study period. The particularly impactful aspect of this study was that similar outcomes were achieved with a median of 10 injections in the faricimab arm and 15 injections in the aflibercept arm—the decrease in treatment burden with faricimab was evident.[13]

A few studies have already reported real-world results with faricimab. TRUCKEE investigated how faricimab fared in a broader treatment population than that included in the trials.[14] TRUCKEE not only included treatment-naïve patients but also those who had already been on anti-VEGF therapy and were switched to faricimab. Notably, after three faricimab injections, mean BCVA improved significantly in previously treated patients with a gain of 2.7 letters. Similarly, mean CST decreased significantly by 38.1 µm. Only one case of IOI was noted after four injections and one case of infectious endophthalmitis, both of which resolved.[14]

A single-clinic retrospective review of 190 eyes that received treatment-resistant nAMD and were switched to faricimab reported that patients who received at least three faricimab injections with at least 3 months of follow-up demonstrated significant improvement in BCVA (~20/43 to ~20/37) and CST (312 ± 87 µm to 287 ± 71 µm).[15] In fact, the mean dosing interval between the last two faricimab injections (7.64 ± 6.2 weeks) was also significantly longer than intervals that were previously achieved with ranibizumab (5.16 ± 2.0 weeks) or aflibercept 2 mg (5.57 ± 3.6 weeks). Moreover, 24% of eyes had no subretinal fluid (SRF) or intraretinal fluid (IRF) at their last clinical visit. We see a recurring theme with faricimab—a decreased treatment burden while maintaining visual and anatomic outcomes. There were no significant adverse events attributed to faricimab in this study.[15]

The Port Delivery System and Brolucizumab

Ankoor R. Shah, MD

Unlike aflibercept 8 mg and faricimab, the port delivery system (PDS) with ranibizumab is a surgically implanted device that enables sustained delivery of ranibizumab. These devices are small; the diameter is 4.6 mm, less than the size of a grain of rice. When implanted in the eye, the flange of the device is covered by the conjunctiva. The PDS was approved by the FDA in October 2021 for the management of nAMD; however, a year later, the manufacturer recalled the implant due to reports of septum dislodgement.

One of the most challenging aspects of the PDS was the refill-exchange procedure. Not only did we need to expend a fair amount of force to perform the refill-exchange, but the physician also had to position the needle precisely perpendicular to the septum to achieve the correct fit that allowed refill-exchange. It's possible that the consequent wear and tear on the septum or, in some cases, incorrect technique led to septum dislodgement. Although new implantations of the device are currently on hold, changes are being made to the implant and refill-exchange needle to optimize the implantation and refill process. We hope there is more to come with the PDS because, having participated in some of the trials, it was encouraging to see that most patients were able to go 6 months without supplemental treatment.[3,4]

By now, we are all familiar with durability the that brolucizumab demonstrated in the HAWK and HARRIER trials.[1,2] Recently, MacCumber et al performed a retrospective cohort study of treatment-naïve and treatment-experienced eyes with nAMD who received treatment with brolucizumab alone for at least 12 months, using the AAO's Intelligent Research in Sight registry.[16,17] Most treatment-naïve and treatment-experienced eyes either had stable or improved visual acuity at 12 months. Among treatment-experienced eyes, only about 30% had a pre-switch interval of 8 weeks or more. This increased to more than 80% following the switch to brolucizumab. The most impressive finding in this study was that up to 55% of treatment-experienced eyes had interval extensions of 4 weeks or greater. However, safety comes first and, in the real-world, safety issues such as IOI and occlusive retinal vasculitis have limited brolucizumab uptake into clinical practice.

Panel Discussion

Dr. Do: The results of the PULSAR trial comparing aflibercept 8 mg against aflibercept 2 mg suggest durability with the higher dose of aflibercept. What is your perception of this durability signal?

Dr. Shah: It's a potentially important solution to the challenges we face in the real world. There are practical constraints to sustaining a high treatment burden and frequent patient visits, so having that durability is very valuable. There are multiple advantages to durability, not the least of which is convenience. I tell patients that if I can get their disease controlled with 10% to 20% fewer injections, their risk for endophthalmitis is also 10% to 20% lower. Their risk for other procedure-related complications is also similarly reduced.

Dr. Scott: The 2-year PULSAR results are promising. All patients with nAMD are a little different, and I feel like some who have particularly high treatment burdens could benefit from this extended treatment duration. I really look forward to having yet another treatment in our armamentarium with these promising early results. We saw some real-world data about the use of faricimab in treatment-experienced eyes or even treatment-resistant nAMD, which begs the question–could faricimab be useful for recalcitrant nAMD?

Dr. Do: Faricimab is a very exciting option because it inhibits both VEGF-A and angiopoietin-2 (Ang-2), both of which are implicated in vascular permeability. I wonder whether the drug's ability to deliver durability, noninferior visual acuity, and the somewhat increased ability to remove fluid is due to the overall higher molar dose of the drug, therefore greater VEGF inhibition, or the Ang-2 moiety. I don't think we know, but it's nice to see those positive results from real-world use, without any concerns about safety. I've certainly used it with my patients, and while the experience is still early, it's a great treatment option.

Dr. Shah: Dr. Scott, what are some of scenarios in which you might consider switching patients to a second-generation therapy?

Dr. Scott: Great question. When aflibercept 2 mg first became available, we were very optimistic. Admittedly, it's a great drug

and continues to be very helpful. However, we thought of it as an every 8-week drug and learned very quickly that there are certain patients who have, for whatever reason, more recalcitrant disease. They would still have fluid, either IRF or SRF, even on the shortest possible interval of 4 weeks. I try to give my patients the longest treatment interval I can and keep the OCT as dry as possible. That, to me, is optimal disease control. Any patient with persistent fluid or optimal disease control but only a 4- to 6-week dosing regimen would be a great candidate for switching to a second-generation therapy.

Dr. Do: Do you reserve the switch to either aflibercept 8 mg or faricimab for eyes that have previously been treated or are you also using them in treatment-naïve patients?

Dr. Scott: I use it in patients who have previously received treatment. I have not yet started any treatment-naïve patients on these medicines. I usually start patients on aflibercept 2 mg, and in my hands, this drug has a reasonable treatment burden for most patients. The patients I cannot extend beyond 6 to 8 weeks are the ones who I will try to switch to newer therapies.

We must still consider the issues we face with the insurance company or payers. We can inform patients about the latest treatment options available, but the payer may mandate that treatment-naïve patients be initiated on a particular drug. It's only once the drug is shown to be unsuccessful, or the patient has had "treatment failure," that we're even authorized to switch. This is something we must keep in mind in these discussions with patients. The decision is not ours alone to make.

Dr. Do: Yes, real-world considerations do factor heavily into the decision to switch. When you do switch patients to either faricimab or aflibercept 8 mg for the first time, are you using any loading doses or proceeding straight into a treat-and-extend (TAE) regimen?

Dr. Scott: I try to simulate the clinical trial scenario as much as I can, to give us the best chances of achieving those clinical trial results. As such, I start with a series of loading doses based upon the clinical trial before I start extending the intervals.

Dr. Do: Great insight, thank you. Along the lines of real-world considerations, we have recently seen the introduction of biosimilars in retina. Dr. Shah, where do they fit in your clinical practice?

Dr. Shah: Great question. I think we will see more biosimilars enter the market as time goes on. They have a role in the treatment of nAMD. I usually use them as part of a progression. For example, as Dr. Scott pointed out, the insurance company may tell us to start with bevacizumab and then work our way up. From there, I might try one of the two ranibizumab biosimilars that are currently available, see how the patient does, and then progress on to aflibercept 2 mg or other therapies, depending on what the payer dictates.

Regarding switching patients, we should be mindful that the frequency of use of these second-generation therapies varies not only between therapies but also depending on the disease state. Brolucizumab, for example, needs to be used every 8 to 12 weeks after the loading doses.[18] For aflibercept 8 mg, the labeling for nAMD states three loading doses followed by at least 7-weekly dosing.[19] You must be cautious about these details because payer policy issues may limit how you can use the drug. With faricimab, the trials showed that 4-weekly dosing was safe, and this was included in the FDA label.[20] This is more akin to how we're accustomed to using our first-generation therapies. So, again, just different nuances to keep in mind in this ever-changing space of retinal medications.

OPTIMIZING TREATMENT INTERVALS

Ankoor R. Shah, MD

The phase 4 RIVAL study was a prospective study, primarily assessing the development of macular atrophy over 24 months when patients with treatment-naïve nAMD were treated with either ranibizumab or aflibercept 2 mg, but on identical TAE

(Continued on page 10)

CASE STUDIES

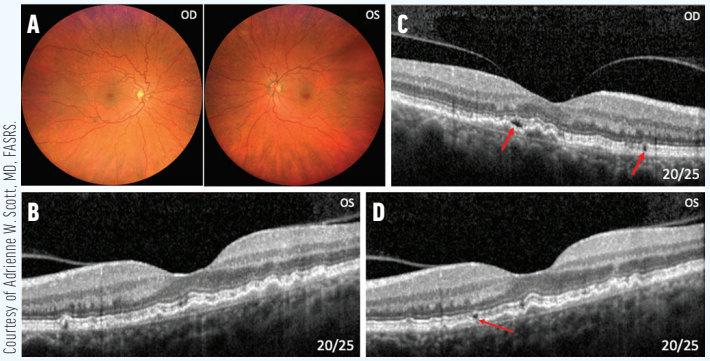
Case 1: Unveiling Asymptomatic Conversion to nAMD

Adrienne W. Scott, MD, FASRS

This 62-year-old woman was referred to me by her oculoplastic surgeon. She had undergone bilateral upper lid blepharoplasty and at the 2-month postoperative visit, she was referred for AMD evaluation. She was asymptomatic and did not have any distortion, but the oculoplastic surgeon very astutely noticed some changes on her fundus exam. The fundus pictures of her right and left eyes show some vascular tortuosity and scattered medium drusen throughout the posterior pole in both eyes (Figure 1A).

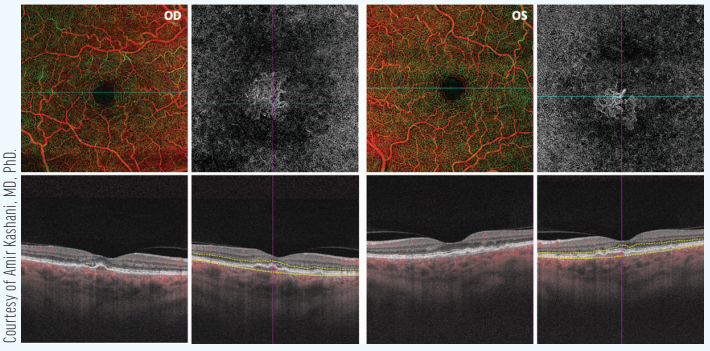
Her VA was 20/25 OU. The OCT image of the right eye showed nice foveal contour, adherent vitreous, no traction, just vitreomacular adhesion (Figure 1B). You can see areas of SRF, which are very mild, and drusenoid pigment epithelial detachments (PED). The left eye looks similar with good foveal contour, drusen, and drusenoid PEDs (Figure 1C). This cut looks pretty good, but in scrolling through the cube, we could see very subtle SRF (Figure 1D). This is a key teaching point. With nAMD, it's important to look through each slice of the OCT cube, even if you think it is dry, because you can pick up more subtle OCT biomarkers.

My next step would have been acquiring a fluorescein angiogram (FA), but this patient presented during the national fluorescein shortage, so I was trying to be judicious about ordering an



Courtesy of Adrienne W. Scott, MD, FASRS.

Figure 1. Fundus photos (A) and OCT imaging (B) of patient referred for AMD evaluation. The red arrows highlight areas of SRF. Areas of SRF in the left eye were only detected upon scrolling through the OCT volume scan (C and D).

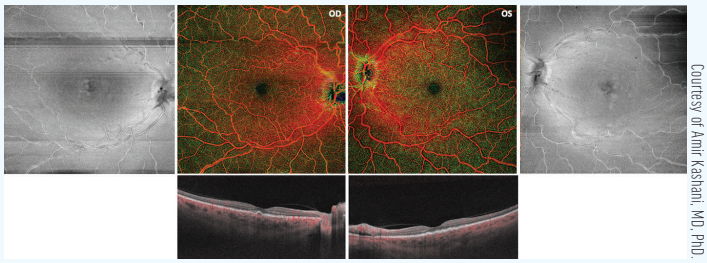


Courtesy of Amir Kashani, MD, PhD.

Figure 3. OCT-A imaging showing foveal CNVM in the right and left eyes of a 62-year-old woman with intermediate AMD.

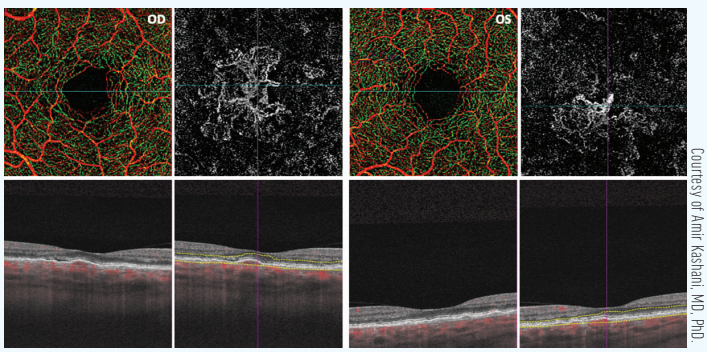
FA. I was fortunate to have access to OCT-angiography (OCT-A) and was able to perform imaging courtesy of my colleague, Amir Kashani, MD, PhD. In these OCT-A images of the right and left eyes, you can see the tortuous vessels (Figure 2). The scan of the choroid of the right shows a choroidal neovascular membrane (CNVM) at the fovea, appearing as a web or net of choroidal neovascularization (Figure 3). Similarly, the left eye is almost a mirror image with a slightly smaller area of a choroidal neovascularization. I zoomed in on a 3x3 slab of the choroid, and you can see the fine detail of the lacy vessels comprising the choroidal neovascular complexes in either eye (Figure 4).

This case was interesting because the patient was asymptomatic, but we saw fluid on the OCT in both eyes, and we were questioning whether to initiate treatment. Could we justify committing an asymptomatic patient to an indefinite treatment course, and the associated time, expense, and treatment burden of bilateral intravitreal injections? The OCT-A was helpful in confirming the presence of CNVMs in each eye. This is termed nonexudative nAMD, and we are detecting more and more of this entity in many of our patients who were previously not thought to have exudative or neovascular disease.



Courtesy of Amir Kashani, MD, PhD.

Figure 2. OCT-A imaging of the right and left eyes of a 62-year-old woman with intermediate AMD.



Courtesy of Amir Kashani, MD, PhD.

Figure 4. A 3x3 slab of OCT-A images of foveal CNVM in the right and left eyes of a 62-year-old woman with intermediate AMD.

In this case, we recommended close observation. I see her every 3 to 4 months and have given her precise home monitoring instructions, so she can detect any distortion or worsening of her vision.

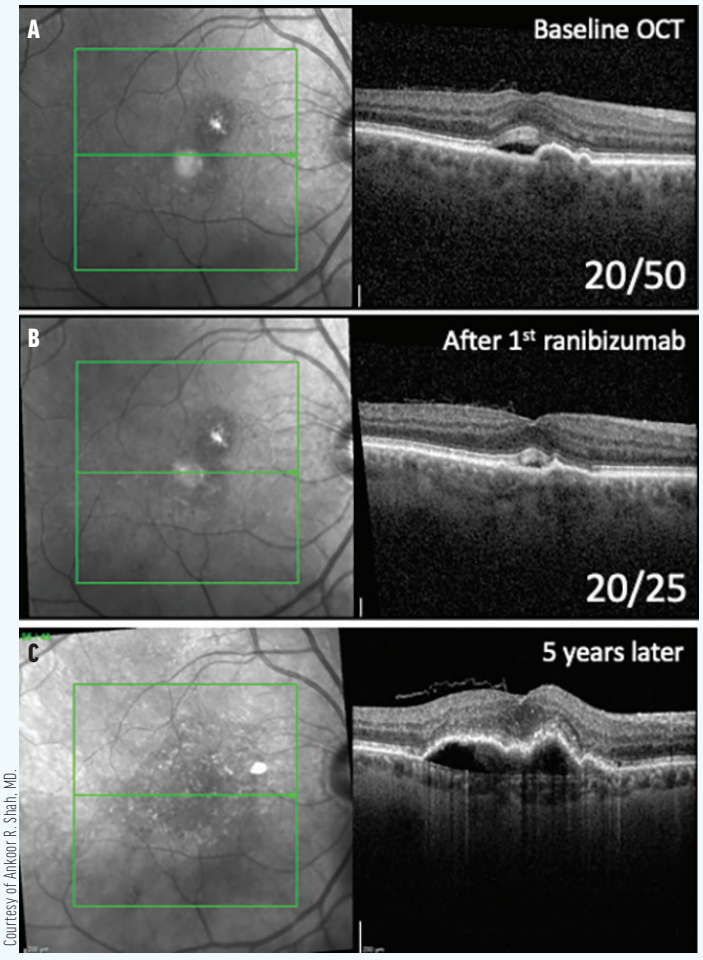
In summary, SRF on OCT can be present in the absence of exudation, and OCT-A can be very helpful in informing the diagnosis and management of these cases. This is one of the areas in which OCT-A can be most helpful in guiding management.

Case 2: A Breakthrough in Resolving Persistent Serous PED

Ankoor R. Shah, MD

This type of case is very common in our clinics. A 63-year-old man presented with 20/50 VA that was distorted in the right eye. In the baseline OCT, you can see the SRF as well as PED (Figure 5A). I also like to order FAs, when available. We did that for this patient (image not shown), after which I started him on ranibizumab (Figure 5B). We saw improvement in the SRF, but you can still see a trace amount. His VA improved to about 20/25, so I continued to treat him with ranibizumab during the next several years. Initially, he was doing well and maintaining q4w intervals; however, eventually, the serous PED started to increase despite being on ranibizumab (Figure 5C).

At this point, I obtained OCT-A imaging to ensure I was not missing any changes in the disease. Unfortunately, our OCT-A images had a fair amount of artifact; you must be prepared for that (Figure 6). Sometimes, as with Dr. Scott's images, you will get



Courtesy of Ankoor R. Shah, MD.

Figure 5. OCT imaging of a patient with nAMD who had SRF and PED at baseline. Although the patient initially responded well to ranibizumab treatment, over the course of 5 years, the serous PED continued to increase.

beautiful nets. Unfortunately, our images did not have that level of detail. However, because of the challenges we were having in extending this patient beyond monthly injections and this worsening of disease, I switched the patient to aflibercept 2 mg.

The patient initially did well on q4w aflibercept; however, during the next year, he developed fluid recurrence again (Figure 7A). This was before faricimab or aflibercept 8 mg were available, so I decided to try double-dose aflibercept 2 mg (Figure 7B). I administered all the aflibercept in the vial and performed a preemptive anterior chamber tap, so the patient was only receiving a total of 0.05 mL over their initial IOP. We started to see improvement in the IRF and serous PED. There is some literature supporting serous PEDs that are refractory to ranibizumab and/or bevacizumab can have a better response to aflibercept 2 mg.[21-23] Unfortunately, this also had to be maintained on a q4w schedule (Figure 7C). Each time we attempted to extend him to q5w, there was fluid recurrence. We were barely controlling it.

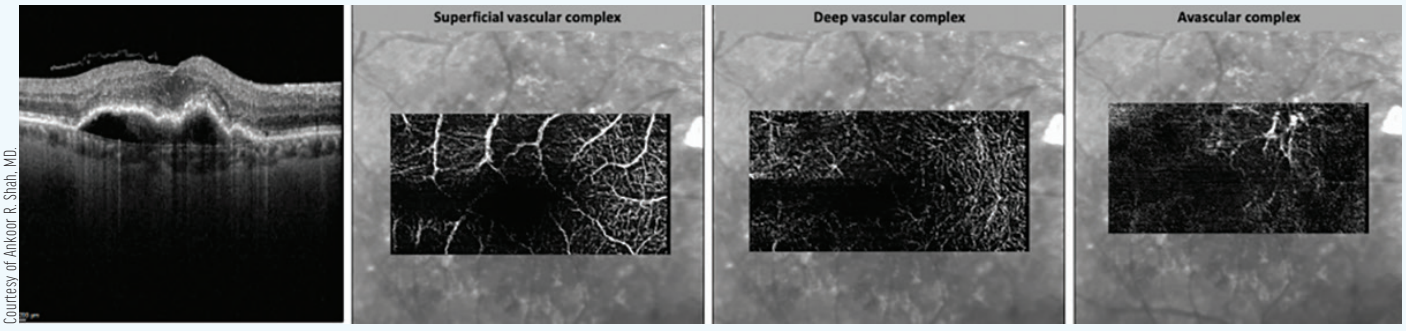
Eventually, the serous PED began to increase. Fortunately, by this point, faricimab was available. This was an ideal case, in my opinion, to switch to faricimab in the hopes of possible interval extension. You can see further improvement of the serous PED and he was extended to 5 weeks (Figure 7D). We only gained an extra week—nowhere close to the 4 weeks seen in the TENAYA and LUCERNE trials—but I think the patient was grateful because it was a 25% reduction in treatment. That is still meaningful from a patient perspective. He was recently switched to aflibercept 8 mg and I hope we will be able to extend him even further.

Panel Discussion

Dr. Shah: I'm curious how you deal with challenging cases like the one I presented—they require a tight level of control and rigid treatment intervals to maintain that control.

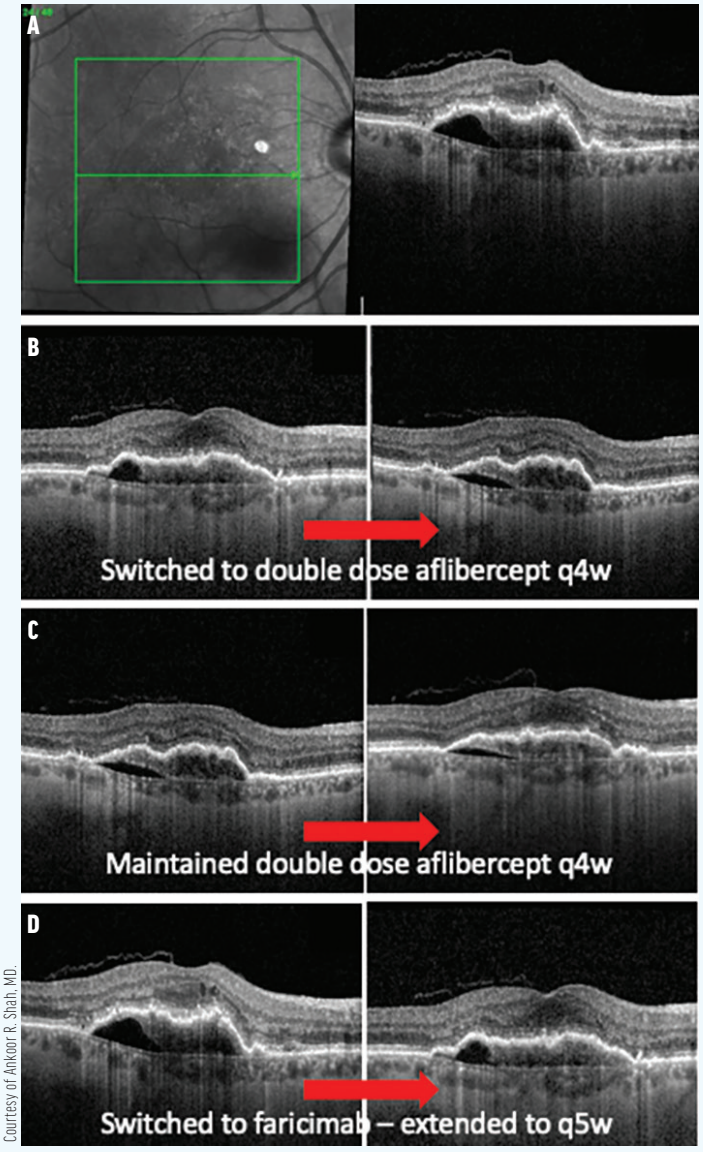
Diana V. Do, MD: We all have these patients who require very frequent dosing of VEGF inhibitors. Your patient did respond to the double dose of aflibercept 2 mg, and I think that is why these second-generation anti-VEGF therapies, some of which have higher molar doses, will be beneficial for many patients who just do not respond that well to conventional treatments. I agree that trialing aflibercept 8 mg could be beneficial in this patient.

Dr. Scott: This was a great case and impressive effort fighting to keep the retina as dry as possible. Our two cases really illustrate the point that the disease can look so different between patients.



Courtesy of Ankoor R. Shah, MD.

Figure 6. OCT-A imaging of a patient with persistent serous PED while on ranibizumab. The images had artifacts and did not provide sufficient detail to guide treatment management.



Courtesy of Ankoor R. Shah, MD.

Figure 7. A patient with persistent serous PED, refractory to ranibizumab and aflibercept 2 mg (A), was treated with double-dose aflibercept 2 mg (B and C) on q4w dosing, which was extended to a q5w dosing regimen when they were switched to faricimab (D).

Dr. Do: We've all also seen cases like the one Dr. Scott presented. It is a bit of a conundrum when you have patients who are asymptomatic, with great vision at 20/25 OU, but you detect some potentially early signs of conversion to exudative AMD. Given the real-world shortage of fluorescein and the patient's vision being so good, I'm not sure the FA would have been necessary. Do you routinely obtain FAs on every new nAMD patient?

Dr. Scott: I do not obtain FAs on every new nAMD patient. I think there are some patients for whom it is helpful to obtain baseline OCT and FA before treatment. For example, if a patient has a significant subretinal hemorrhage but I'm not sure where the leakage is focused, an FA is helpful so I can understand the characteristics of the patient's CNVM and evaluate their response to treatment. I'm trying to become more facile with OCT-A. Dr. Shah's point about OCT-A images is very well taken. I shared some beautiful images that were taken using a research protocol that Dr. Kashani shares with our faculty at Wilmer Eye Institute; however, not all OCT-A images are as easy to interpret. There is still a learning curve. I think OCT-A will be used more frequently as physicians become more facile with the technology and software platforms improve.

Dr. Do: Speaking of understanding lesion characteristics, what is the role of ICG in your practice, Dr. Shah? I can't remember the last time I ordered an ICG, but do you think it is useful for particular types of lesions?

Dr. Shah: I don't order an ICG that often—probably a handful of times a year. It does have a role in certain scenarios such as polypoidal choroidal vasculopathy, where you might like to visualize the polyp and see what's going on. Even in this case, while my counselling would change, my treatment regimen does not necessarily change much, so I usually still prefer FAs. For example, ICG can be helpful for a 55-year-old patient who you suspect could have central serous chorioretinopathy rather than AMD. If the enhanced depth imaging on the OCT does not show a clear difference in choroidal thickness and you need a tie breaker to help make the call, ICG is useful.

(Continued from page 7)

regimens.[24] While there were no significant differences between the two groups in the rate of development of macular atrophy over the study period, an interesting observation from the study was the proportion of patients that were fluid-free (IRF and SRF). There were no significant differences between ranibizumab and aflibercept 2 mg in the proportion of patients with a completely dry retina at 12 or 24 months; however, approximately 40% of all patients still had some retinal fluid despite very strict TAE regimens.[24] Herein lies the challenge—our first-generation therapies are very good, but there remains an unmet need for several patients who do not achieve optimal disease control.

In clinical practice, regardless of whether we use first- or second-generation therapies, treatment regimens must be flexible to meet the demands of the real world and disease activity of individual patients. While there are several different dosing regimens that can be used, TAE regimens are proactive, individualized, avoid overtreatment and undertreatment, and optimize functional and anatomic outcomes. Because patients receive injections at every visit, treatment plans can be adapted accordingly. The customizability offered

by this dosing strategy is important, but how can we determine the optimal parameters of a TAE regimen? ALTAIR and ARIES were trials that used a pragmatic approach to investigate two aspects of TAE regimens. ALTAIR asked whether we should be using 2- or 4-week extensions, and ARIES looked at whether the timing mattered regarding when the TAE regimen was initiated.[25,26]

At 96 weeks, in the ALTAIR trial, the mean number of aflibercept 2 mg injections in the 2- and 4-week groups were almost identical at 10.4 ± 2.6 and 10.4 ± 2.4, respectively.[25] At weeks 52 and 96, the mean change in BCVA and CRT were very similar between the groups. At week 96, the mean last interval was 12.2 ± 3.6 and 12.5 ± 3.6 weeks in the in the 2- and 4-week groups, respectively. In fact, by week 96, 57% and 60% of patients had dosing intervals of 12 weeks or greater, and 42% and 46% of patients had intervals of 16 weeks or greater, respectively.[25]

In the phase 3b/4 ARIES trial, patients received four monthly loading doses of aflibercept 2 mg and were then randomized for an "early-start" TAE regimen with 2-week interval adjustments or a "late-start" TAE regimen, which involved 8-week dosing until week 48, followed by 2-week interval adjustments.[26] There were a few key data points from this trial. The mean number of injections at 104 weeks was very similar (12.0 for early-start and 13.0 for late-start), with a difference of one injection; 47.2% of patients with the early-start TAE regimen could be extended to intervals of 12 weeks or greater, compared to almost 52% of patients in the late-start TAE group.[26] The key takeaway from this trial appears to be that the timing of TAE initiation does not matter.

One of the key differences between ARIES and ALTAIR was that they had different retreatment criteria. For example, ALTAIR included an option for patients to be maintained on their current injection interval if they had residual but decreased SRF.[25] On the other hand, ARIES had no maintenance criteria.[26] This remains an ongoing challenge, not just for these trials, but when we try to make interpretations or comparisons across trials. For example, across the second-generation therapies that are commercially available—aflibercept 8 mg, faricimab, and brolucizumab—the disease activity assessment criteria in the TENAYA, LUCERNE, PULSAR, HAWK, and HARRIER trials were all different. They used multiple measures of disease activity—most commonly changes in BCVA, retinal thickness on OCT, the presence of fluid and/or macular hemorrhage/neovascularization—and there were differences between how these measures were implemented.

One thing I would personally like to see in clinical research trials is a standardization of this approach. It would allow better comparability between trials. Currently, varied approaches mean varied results. For example, it would be unfair to compare the topline data between aflibercept 8 mg in PULSAR to that of faricimab in TENAYA and LUCERNE. We see different proportions of patients who achieved and maintained q16w dosing during the first year, ie, 77% in PULSAR and 45% in TENAYA and LUCERNE. However, as we know, the trials had different criteria for disease activity and retreatment. Therefore, in the absence of head-to-head randomized controlled trials, it is dangerous to make direct comparisons between the drugs and the outcomes they can deliver.

What is encouraging, regardless of the trial or drug, is that there were a notable number of patients across all trials that could be extended to longer durations. That is the key underlying takeaway when looking at both drugs/trials. We hope that the field will move toward achieving some sort of disease activity assessment consensus, so that there is opportunity to make unbiased and informed comparisons across different trials.

DEEP DIVE INTO OCT BIOMARKERS IN nAMD

Adrienne W. Scott, MD, FASRS

Gauging disease activity in nAMD can sometimes be challenging. There are functional and anatomic aspects, both of which are important and routinely considered. Functionally, BCVA is easy to measure and a criterion that is carefully monitored in real-world treatment as well as an efficacy measure in clinical trials. It is well known that baseline BCVA is highly prognostic of long-term treatment outcomes. While BCVA is a subjective measurement that is heavily reliant on patient cooperation and cognitive involvement, it is the most important aspect of the disease to the patient. It's a metric they understand. It's what the DMV checks when they go to get their driver's license. Clinically, however, BCVA may or may not correlate to the anatomic measures of disease activity.

The AAO recommends using OCT-based criteria as markers of lesion activity.[27] For us as physicians, anatomic outcomes are important because they are objective, directly measured using imaging, can be evaluated both qualitatively and quantitatively over time, and do not require much patient cooperation, cognition, or comprehension. They are usually the gold standard by which we gauge disease activity. When deciding which patients to extend or how long to extend them, we tend to rely more on anatomic measures than vision. However, imaging biomarkers have limited predictive value compared to the predictive power of BCVA. Moreover, there is no real consensus on the clinical significance of some anatomic features of disease activity. For example, we continue to have debates over how much fluid we tolerate on OCT and whether fluid location matters.

While there are several prognostic biomarkers on OCT, a few key ones include retinal fluid, PED, hyperreflective foci (HRF), and subretinal hyperreflective material (SHRM), all of which are uniquely significant to disease prognosis.[28] Of these, retinal fluid is the anatomic measure that we routinely assess as it plays a big role in our treatment decisions. Indeed, when asked which potential benefits of long-lasting anti-VEGF therapies were the most important, approximately 80% of respondents to the 2023 American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) survey chose longer maintenance of the drying effect.[29] Almost 50% of respondents also highlighted the importance of less fluid variation over time and reduction in fluid volume volatility between injections.[29]

We have a better understanding now that not all fluid compartments are equally deleterious, and some are more poorly tolerated than others. Moreover, as discussed in Case 1, not all fluid is linked with exudation and this distinction is important for treatment

decisions. Five-year data from the CATT trial showed that overall, eyes with macular fluid had lower visual acuity than those without.[30] More specifically, IRF had a much greater negative impact on visual acuity than SRF or sub-RPE fluid at all time points. In fact, eyes without SRF had similar vision to eyes with SRF, suggesting that some residual SRF can be tolerated. Post hoc analyses of the HARBOR, VIEW 1/2, ARIES, and ALTAIR trials have all shown that the presence of SRF was associated with better BCVA, particularly if not associated with IRF.[31-35]

Based on these data, the randomized controlled FLUID trial prospectively assessed whether patients treated with ranibizumab on a "relaxed" TAE regimen (some SRF tolerance at foveal center, no IRF tolerance) could achieve similar BCVA outcomes as those on an "intensive" TAE regimen (no fluid tolerance).[36] The trial showed that over 24 months, the mean change in BCVA in the "relaxed" group was noninferior to that seen in the "intensive" group (2.6 ± 16.3 letters vs 3.0 ± 16.3 letters, respectively), with similar proportions of patients in both groups achieving 20/40 VA or better. The "relaxed" group received significantly fewer injections (15.8 ± 5.9 vs 17.0 ± 6.5) and significantly more participants could be extended and maintained on q12w dosing (29.6% vs 15.0%). Conversely, significantly more participants in the "intensive" group did not extend beyond 4-week intervals (13.5% vs 2.8%).[36] Therefore, patients who were treated with ranibizumab on a TAE regimen who tolerated some SRF had comparable visual outcomes with fewer injections to those who were treated with the intention of complete fluid resolution.

Somewhat in opposition to that school of thought, a post hoc analysis of the HAWK and HARRIER trials evaluating brolucizumab 6 mg against aflibercept 2 mg found that the absence of any type of retinal fluid at more clinic visits or lower levels of any fluid after the loading phase were positively associated with visual and anatomic outcomes.[37,38] Looking at pooled patient-level data from both study arms, patients were assigned to one of five categories based on the number of fluid-free visits.[37] Those who were always dry or almost always dry consistently had the best visual and anatomic outcomes at week 96. These patients also had the lowest variability in retinal thickness over time. Conversely, patients who were never dry or had very few fluid-free visits consistently had the worst visual and anatomic outcomes.[37]

As a community, we are still determining the clinical relevance of fluid findings. There are many analyses being done with second-generation therapies that look at parameters such as time to fluid resolution or degree of fluid resolution. For example, in the TENAYA and LUCERNE trials, the cumulative incidence of first absence of IRF and SRF was at week 8 for faricimab after two injections and week 12 for aflibercept 2 mg after three injections.[39] While these early data suggest that faricimab is drying the retina more quickly and with less of a treatment burden, it remains to be seen whether this difference is meaningful in the real world. As we gather more data from randomized controlled trials that specifically look at the effect of different fluid compartments in the retina, our perspective on fluid control in nAMD will grow and change.

Panel Discussion

Dr. Do: Do you try to remove all SRF or do you tolerate small amounts of SRF?

Dr. Scott: I try to remove as much as I can. The presence of SRF is usually my impetus for shortening a treatment interval. However, you will have some patients who never dry completely. You can treat them diligently every 4 weeks with your agent of choice but they continue to have SRF. In those cases, I tolerate some SRF but I do try to eradicate as much as I can. A patient with persistent fluid may make me think about switching to a different agent that has shown to be a little bit more effective in drying out the retina. What are some biomarkers on OCT that are particularly concerning to you and influence your treatment decisions?

Dr. Shah: Some OCT biomarkers help determine how the control is going more than others. For me, IRF, SRF, and hemorrhage are the top three, but there are differences in how you counsel patients based on these biomarkers. While they all vary in terms of clinical significance, IRF is one that universally tends to have worse outcomes and can be tougher to treat. We're continuing to learn more about all these prognostic factors and how they can help guide that discussion with our patients.

Dr. Do: I'm also more likely to switch to another therapy if there is persistent IRF. If that does not go away with the agent I am using at the time, I recommend switching early on.

PANEL DISCUSSION: The Evolving Landscape in nAMD

Diana V. Do, MD: We have discussed newer therapies. The pipeline is also very exciting; there are agents targeting new mechanisms of disease as well as new routes for delivering therapies.

Sozinibercept (previously known as OPT-302) is a soluble fusion protein that binds and sequesters VEGF-C and -D. These VEGF isoforms not only activate the VEGF receptors (VEGFR-1 and -2) that are activated by VEGF-A, but are also the only isoforms that activate VEGFR-3, which is also implicated in nAMD for facilitating pathological angiogenesis and reducing vascular permeability.[40] As such, sozinibercept is being evaluated in clinical trials as an adjunct therapy, ie, physicians would be giving patients two separate injections, one for sozinibercept and another for either ranibizumab or aflibercept 2 mg.

In the phase 2b trial in treatment-naïve patients with nAMD, patients were either treated with ranibizumab monotherapy or sozinibercept in combination with ranibizumab.[40] The trial demonstrated that combination therapy resulted in significantly superior mean visual acuity gains compared to ranibizumab monotherapy (14.2 ± 11.6 letters vs 10.8 ± 11.5 letters, respectively). There were also no safety signals with combination therapy compared to monotherapy.[40] The phase 3 SHORE and COAST trials for sozinibercept are unique because they are powered for superiority in visual acuity outcomes, which is a high bar to overcome. SHORE will evaluate sozinibercept in combination with ranibizumab, while COAST will evaluate sozinibercept in combination with

aflibercept 2 mg. Both trials are currently enrolling patients with topline data expected in 2025.

Another exciting area of clinical development is gene therapy. ABBV-RGX-314 is a viral vector-based therapy encoding a soluble ranibizumab-like protein, and is intended to be a one-time treatment. In the phase 1/2a study, it was delivered subretinally (requiring vitrectomy) and in the ongoing phase 2 AAVIATE trial, it is being delivered via suprachoroidal injection. Early clinical trial data looks very promising in reducing the treatment burden. While it does not eliminate the need for supplemental anti-VEGF injections in every patient, it can reduce the number of future injections. A pivotal study, ATMOSPHERE, to evaluate both efficacy and safety is ongoing. Dr. Shah, what are your initial thoughts about this vector-based therapy?

Dr. Shah: It's very interesting because if this pans out, we're approaching a "one-and-done" treatment where we set up a bio-factory within the eye that continuously produces anti-VEGF. When I talk to patients about these trials, I explain it in terms of the adage of teaching a man to fish versus giving a man a fish. It's a very different approach and there's a lot to unpack, but the idea is sustained VEGF inhibition. What we need to track is how this sustained production of anti-VEGF fares and is tolerated long-term.

I've only done a few of these surgeries. The subretinal space is relatively familiar to vitreoretinal surgeons. While there are some tricks to the procedure, most patients do well. One of the things that we've been monitoring in the posttreatment period is the development of pigmentary changes. It is unclear why this develops.

The early data, however, are impressive, especially if it means that a notable proportion of patients can come off injections entirely and the rest at least see a significant reduction in treatment burden. From a societal perspective, given the number of injections we currently administer in patients with nAMD, there is a need for treatments that reduce or eliminate injections entirely. This would be a great opportunity to do that, so looking forward to the results.

Dr. Do: Another drug that's being evaluated is CLS-AX, a tyrosine kinase inhibitor (TKI) delivered via the suprachoroidal space. In the phase 1/2 OASIS trial, there was a positive response in some of treated eyes that saw a reduction in treatment burden. There's an ongoing extension study and future pivotal clinical trials that will evaluate whether TKIs truly do decrease the treatment burden, and can also help maintain and/or improve vision.

Approximately 80% of respondents to the 2023 ASRS PAT survey stated that both better long-term vision outcomes and longer maintenance of a drying effect were equally important to them when considering newer anti-VEGF agents.[29] Based on the data we are seeing with existing and pipeline therapies, we may be a little closer to achieving both goals. ■

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Years in Practice
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___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week
(with the disease targeted
in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
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___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Describe the current treatments available to treat neovascular age-related macular degeneration (nAMD)	_____	_____	_____
Discuss the considerations involved in the choice of anti-VEGF agent and tailoring treatment regimens for individual patients	_____	_____	_____
Evaluate clinical evidence for biomarkers that are prognostic of optimal visual outcomes	_____	_____	_____
Summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in nAMD	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in neovascular age-related macular degeneration (nAMD) (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. According to the PULSAR trial, which of the following statements is TRUE?

A. Aflibercept 8 mg dosed every 12 or 16 weeks was inferior to aflibercept 2 mg dosed every 8 weeks
B. Aflibercept 8 mg dosed every 12 or 16 weeks was superior to aflibercept 2 mg dosed every 8 weeks
C. Aflibercept 8 mg dosed every 12 or 16 weeks was noninferior to aflibercept 2 mg dosed every 8 weeks
D. Aflibercept 8 mg dosed every 12 or 16 weeks was equivalent to ranibizumab dosed every 8 weeks

3. A 64-year-old man presents to your clinic with a chief complaint of visual distortion. On examination you note 20/50 VA in his right eye. Fundus examination reveals thickening in the macula. OCT angiography shows a drusenoid pigment epithelial detachment (PED) with adjacent subretinal fluid. You decide to inject him with monthly ranibizumab, but the size of his PED continues to increase, along with increasing cystic intraretinal fluid. All of the following are reasonable next steps in management of this patient EXCEPT:

A. Switch to intravitreal aflibercept 2 mg
B. Switch to faricimab
C. Switch to intravitreal aflibercept 8 mg
D. Maintain on monthly ranibizumab

4. You are evaluating a 72-year-old woman with nAMD. She is currently receiving intravitreal aflibercept 2 mg and is on a treat-and-extend protocol. Her last injection was 6 weeks prior. On examination, you note a new macular hemorrhage and increased cystic intraretinal fluid on her OCT compared to her prior imaging. She was previously maintained well on monthly aflibercept. Which of the following is the next best step in management of this patient?

A. Extend treatment interval by 2 weeks
B. Extend treatment interval by 4 weeks
C. Shorten treatment interval by 2 weeks
D. Shorten treatment interval by 4 weeks

5. Which of the following retinal fluid types has the most negative impact on visual acuity?

A. Persistent intraretinal fluid
B. Persistent subretinal fluid
C. Subretinal pigment epithelial fluid
D. Nonpersistent subretinal fluid

6. You are managing a 74-year-old patient with nonexudative AMD. You note subtle changes on OCT in her retinal anatomy and are concerned that she is developing exudative AMD. Due to a fluorescein shortage, you cannot obtain a fluorescein angiogram. What is the next best step?

A. Obtain fundus autofluorescence
B. Obtain OCT angiography
C. Obtain B-scan ultrasound
D. Obtain fundus photography

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this 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 consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
You would recommend this program to your colleagues	___ Yes	___ No

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

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

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