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THE AMD TREATMENT BURDEN: CURRENT STATUS AND PROMISING SOLUTIONS

Provided by evolve medical education

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CONTENT SOURCE

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

ACTIVITY DESCRIPTION

Newer classes of drugs are being evaluated to treat age-related macular degeneration (AMD), along with longer duration of currently approved drugs. This supplement reviews the expanding therapeutic innovations and improved diagnostic technologies.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists and retina specialists involved in the treatment and management of patients with retinal diseases.

LEARNING OBJECTIVES

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

- **Describe** the differences in real-world clinical outcomes with those from prospective clinical trials.
- **Develop** individualized treatment regimens for patients with AMD who may benefit from treatments with longer duration.
- **Discuss** newer compounds in development or recently approved compounds that are designed to improve visual outcomes while decreasing treatment burden.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation.

1. Please rate your confidence in your ability to manage patients with AMD (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. Please rate how often you apply the latest treatments in AMD (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. Typically, the biggest cited unmet need in the treatment of wet AMD is _____.

a. Agents at a lower cost
b. Personalization
c. Remote monitoring of fluid levels
d. Drug durability

4. A 76-year-old female with wet AMD has received monthly injections with aflibercept for the past year. She travels 3 hours roundtrip with a caretaker for her appointments and has indicated this might be difficult for her caretaker to maintain. Her vision is 20/40 and stable. She has persistent subretinal fluid that has not resolved. Which of the following may offer her the same quality of treatment but reduce the treatment burden?

a. Switch to brolucizumab
b. Nothing; the subretinal fluid is not impacting her vision yet, so monthly injections are still needed.
c. Recommend gene therapy
d. Order fluorescein angiogram and indocyanine green chorioangiography at her next appointment, because it could be a misdiagnosis.

5. What is the recommended first-line treatment for an 80-year-old male with a high PED and associated intraretinal fluid?

a. Generic bevacizumab
b. A branded anti-VEGF
c. Laser photocoagulation
d. Intravitreal corticosteroids

6. A 75-year-old female has a small amount of hemorrhage with a PED. Do you need to completely flatten the PED during treatment?

a. No. There is a possible risk of geographic atrophy with PED flattening.
b. Yes. The patient will achieve a higher BCVA if the PED is flattened.
c. No. The patient will lose vision if the PED is flattened.
d. Yes. There is no risk for geographic atrophy if the PED is flattened.

7. Brolucizumab is under ongoing investigation for safety because of what associated adverse event?

a. Inflammation
b. Glaucoma
c. Retinal Arterial occlusion and Occlusive Vasculitis
d. Retinal detachment

8. A 70-year-old female patient with wet AMD and no significant comorbidities has had a good response to quarterly ranibizumab for the last 18 months. Her vision is 20/30. She is starting to ask how many more injections are needed and seems interested in fewer appointments. All but which are potential options to consider?

a. Switch to aflibercept
b. Switch to brolucizumab
c. Stay with quarterly injections of ranibizumab and stress the importance of compliance
d. All of the above

9. What are the potential barriers to the gene therapy RGX-314? *Select all that apply.*

a. It requires a vitrectomy in the operating room
b. Drug durability isn't long enough
c. Learning curve for physicians
d. Poor efficacy

10. In what clinical scenario is some subretinal fluid acceptable?

a. Subretinal fluid is never a concern and can protect vision in some patients.
b. Only after three loading doses is subretinal fluid acceptable; beyond that it must be treated aggressively.
c. In patients with good, stable vision after maximum therapy a small amount of fluid is acceptable.
d. Subretinal fluid should always be treated aggressively.

The AMD Treatment Burden: Current Status and Promising Solutions

The approval of anti-VEGF agents for the treatment of age-related macular degeneration (AMD) in the early 2000s ushered in a new era for AMD management. No longer were patients rapidly going blind from their disease; consistent anti-VEGF injections preserved the sight and improved the quality of life of millions of patients.[1] However, despite significant progress in treatment paradigms, AMD remains the leading cause of irreversible blindness worldwide.[2] Patients are saddled with lifelong eye injections, leading to significant treatment burden, financial strain, loss to follow-up, and poor visual outcomes if frequent treatment is abandoned. Clearly, the next step in advancing AMD treatment is drug durability. A number of novel approaches are in the pipeline, including sustained-release devices and gene therapy. The following continuing medical education activity brings together thought leaders in retina to discuss clinical challenges in AMD management and treatment advances on the horizon.

—Arshad M. Khanani, MD, MA, Moderator

AMD MANAGEMENT IN THE REAL WORLD

Q | ARSHAD M. KHANANI, MD, MA: When a patient presents with neovascular AMD, what do you discuss with them initially? How are you currently managing these patients?

MICHAEL SINGER, MD: My initial discussion depends on how the patient presents to me. If the patient comes in de novo and knows very little about AMD, we'll discuss what it is and the differences between wet and dry. I'll explain that dry is much more common at 85% to 90% of all cases, but wet is more severe and leads to vision loss.[3] After a clinical examination, I'll perform fluorescein angiography (FA) and optical coherence tomography (OCT) to see how much fluid he or she has and determine what kind of AMD it is.

We'll then discuss injections, and I'll explain that there are a number of different medicines on the market. When I say the word "shot," patients are typically very taken aback because no one expects to get a shot in their eye. I try to make them feel more comfortable by explaining that we give an anesthetic, and that it will not hurt much. I emphasize that AMD treatment is continued therapy and that it's not one and done; they will receive a series of injections over time. Finally, I explain that we will watch them very carefully and monitor them based on how their disease responds.

DR. KHANANI: Most physicians give AMD patients loading doses and then move to a treat-and-extend paradigm. How can we ensure patients stay compliant with the treatment? What can physicians do to improve this?

CHRISTINA Y. WENG, MD: Our ability to achieve and maintain visual gains is often hampered by loss to follow-up and a lack of compliance.[4] The first two questions patients often ask are "Will the injection hurt?" and "How many injections will I need?" I explain that AMD injections are like brushing your teeth. No matter how well you brush today, you're going to have to brush tomorrow. They will likely receive injections for an extended period to maintain their visual gains and protect their vision.

It's critical to manage patient expectations early on. Many patients develop injection fatigue when they plateau after initial visual improvements and start to think injections are no longer necessary.[5] I explain from the start that vision stabilization is the primary goal, but that hopefully we will also achieve visual gains. I make it very clear that without therapy, neovascular AMD will certainly lead to vision loss[6]; therefore, it's critical they do their part and are compliant with injections.

CARL DANZIG, MD: When I first meet a patient, I tell them they will need a certain amount of injections in the first 2 years of treatment. If you look back at the original clinical trials, patients received injections every 4 weeks for 2 years.[7-10] Even with the best treatment, their vision may decline. But if they don't keep their appointments, that decline is guaranteed.

Building a rapport with a patient and giving them a realistic outlook is very important early on. We know that patients in the real world don't have the same outcomes as patients on clinical trials.[11] One in five patients will be lost to follow-up after the first treatment.[4] Real-world patients have real-world problems. They get sick and are hospitalized; they are elderly and struggle to come to the clinic; they live in different locations; and the weather and time of year can also have an impact. There are many reasons patients fall off over time.

DR. SINGER: At the beginning of the patient relationship, you want to explain that this is a journey. The AMD patient population is older and has a lot of comorbidities.[12] A 2-year, retrospective, case-control study of 26,057 Medicare beneficiaries enrolled from Jan. 1, 2003, to Dec. 31, 2004, found that nearly all patients had at least one comorbidity and 80% had five or more comorbid conditions.[12]

There are many factors for why patients can't make it into the clinic. Data shows that clinical trial results don't translate into the real world. Patients in the HORIZION and VIEW 1 extension studies[10,13] had phenomenal results on monthly treatments, but over time as their interval increased, their vision declined.

We have impressed on patients and their families that our goal is to stabilize vision. We know that when patients receive fewer shots, they lose vision.[14] For example, the SEVEN-UP study pooled outcomes from the ANCHOR, MARINA, and HORIZON trials. The patients who received an average of 6.8 injections of ranibizumab lost vision, while patients who received 11 or more injections gained letters.[8] The AURA study also showed a correlation between the number of injections given and number of letters gained.[15]

DR. KHANANI: I agree with our comments about vision loss in the real world. We recently published the SIERRA-AMD study.[11] The goal was to characterize real-world baseline visual acuity (VA) and anti-VEGF treatment patterns in AMD patients between 2012 and 2015 in almost 100,000 eyes of nearly 80,000 patients. In eyes with 4-year follow-up, VA changes from baseline (ETDRS letters) were least squares means of +1.1 (95% confidence interval [CI], 1.0;1.3), −1.3 (95% CI, −1.5;−1.0), and −3.1 (95%CI, −3.5;−2.7), and −5.2 (95% CI, −6.0;−4.3) for years 1 through 4. Mean ± SD number of injections was 7.5±1.9, 6.7±2.1, 6.6±2.3, and 6.4±2.3 for years 1 through 4.[11] That being said, Anti-VEGF agents have revolutionized the way we manage AMD patients and have saved the sight of millions. What are some of the drawbacks to these agents?

DR. WENG: As recent as the late 1990s and early 2000s, a wet AMD diagnosis was a blind sentence. So to now have anti-VEGF agents that work very effectively is wonderful, and the fact that the discussion has shifted from efficacy to treatment burden is a testament to how far we've come. When I think about drawbacks to these agents, three things come to mind: durability, treatment approach, and cost.

In my opinion, the biggest drawback is durability. Anti-VEGFs work well, but the treatments are relatively short-acting; patients don't enjoy the sustained visual changes we hope for, and there are many opportunities for attrition. We know from real-world studies that patients' visual gains can drop off with time.[11,15] Longer-acting agents would allow us to improve care and achieve the visual gains we know are possible with consistent and frequent dosing.

The second drawback is our one-size-fits-all approach. We're not yet able to individualize treatment aside from the interval. Some patients do well, while others are less responsive to treatment and continue to lose vision. Wet AMD is a complex multifactorial disease, and we don't fully understand the intricacies of the pathogenesis and its genetic drivers. As we learn more, I hope we can begin tailoring therapies to individual patients.

The third drawback is cost. Anti-VEGF agents are very expensive for patients and for our health care system. Twelve months of ranibizumab will cost more than $11,000 in a treatment-naïve patient, while 12 months of aflibercept costs just over $10,000.[16] Although cost is not, and should not be, the primary factor that drives treatment choice, it is an important consideration when you're talking about treating the disease at a population level.

Q | **DR. KHANANI:** Excellent points. All those factors are important and that's why most of us in the United States use a treat-and-extend approach to decrease treatment burden and clinic visits. The biggest unmet need in my opinion is durability.

Let's switch gears and talk about disease management. All of us monitor AMD based on OCT imaging. When you're treating a patient with neovascular AMD, how do you know you're controlling the disease? What signs of success do you look for on the OCT?

DR. DANZIG: OCT drives treatment. Spectral-domain OCT has enabled us to find small amounts of fluid in different retinal compartments. We have to determine the proper treatment interval once they get out of the loading dose phase. Every time a neovascular AMD patient comes in, they get an OCT, even if it is an injection-only visit. I like to be able to monitor their fluid status. I want to see how they respond from visit to visit, and how they've responded from baseline. We know from the HARBOR post-hoc analysis that patients who had a little residual subretinal fluid (SRF) without the presence of intraretinal fluid (IRF) actually did better than the patients who were completely dry.[17]

In the real world, however, when I see a patient with fluid, I feel uneasy. I know that if the fluid is stable over multiple visits and their vision is good, it may be okay to keep that patient at that interval. The presence of fluid and the amount of fluid that's acceptable is an ongoing debate; we're still learning the parameters and what it means for the patient. Some patients may be fine with fluid, while others may not. This is why we have to find ways to tailor treatment.

DR. KHANANI: I agree; OCT is our primary modality to evaluate disease activity. Obviously, VA is also important, but I think it varies too much in the real world and can be unreliable at times. Even during clinical trials, there's published data that shows patients can have variability of five or more letters day-to-day.[18] The persistent fluid is an interesting question. Our goal should be to dry intraretinal and SRF while decreasing treatment burden. If a patient has persistent SRF, stable disease, and good vision with the maximum therapy, I try to extend the interval.

There is also new data on aflibercept looking at different fluid compartments. Does the fluid type matter? How much fluid is okay?

DR. SINGER: We looked at people in the VIEW study who were dry after the first 3 months, people who weren't dry all the time, and after the three loading doses. When you look at the loading dose, only about 25 to 30% of people were persistently dry over all three loading doses. We discovered a few things by examining the loading dose. First, if people were dry for all three visits versus people who had fluid at any point, they had much better scores on the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). It turns out that people with residual SRF had the best vision overall and patients with IRF seemed to have worse vision.[19]

This same finding regarding IRF and SRF was seen in the HARBOR study. A subanalysis was conducted looking at different fluid compartments for patients who obtained 20/40 or better at 12 and 24 months. Patients with residual SRF had the best vision while patients with IRF had the worst vision. So chronic SRF may not be as bad as we think. I want to be clear: this is chronic SRF and I believe that there are probably different mediators in the shadow we see on OCT in patients with chronic SRF than patients with acute SRF.[20]

DR. KHANANI: In these trials, patients received maximum treatment. Because they received maximum treatment and still had fluid, we have to live with it. I think if we can dry the retina better or if we can have an agent that can modulate another pathway and better control the disease, we may be able to improve our treatment outcomes in terms of durability and efficacy.

CHALLENGES AND CONTROVERSIES IN AMD MANAGEMENT

Q | DR. KHANANI: How do you handle pigment epithelial detachments (PEDs) in AMD patients?

DR. WENG: PEDs are challenging because we don't have robust data to guide treatment. PEDs occur when the retinal pigment epithelium (RPE) separates from the underlying Bruch membrane as a result of fluid accumulation or other materials.[21] Although as many as 66% of eyes with AMD develop PEDs,[22] the majority of our clinical trials have either not included eyes with PEDs or have not been designed to evaluate the treatment response of PEDs specifically.

The approach to managing a PED varies widely amongst retina specialists. If a PED has associated intraretinal or SRF, I treat with anti-VEGF. Bevacizumab, ranibizumab, and aflibercept have all been found to reduce PED size and stabilize vision,[23,24] although VIEW and CATT illustrated that the resolution can be slow and incomplete.[25-27]

I tend to use the branded drugs, especially aflibercept, for PEDs because I find they work better than bevacizumab, based on my own experience. I typically reserve bevacizumab for neovascular AMD patients without a PED. I don't think that completely flattening PEDs is necessary. In fact, there's some scientific evidence to suggest that complete flattening could be detrimental and actually increase the rate of atrophy development.[28,29]

Decision-making is most challenging when a patient has a PED with no associated fluid. In these cases, ancillary imaging with FA or OCT angiography (OCTA) can be helpful in discerning the PED subtype. We've all seen patients who maintain excellent vision, even if the PED is very high. I've always found it interesting that VA doesn't seem to correlate with PED height at all. Some suggest that injecting PEDs frequently may increase the incidence of RPE tears, but this is difficult to assess because PEDS are inherently at a higher risk of this occurring, especially at greater PED heights.[30]

DR. SINGER: The PrONTO study set the stage that treating PEDs alone without fluid doesn't improve outcomes in patients.[31] Most of these patients have good vision, and RPE tears can happen without treatment. I do think the PED height is directly correlated with the risk of RPE tear.[28]

There is a study that showed aflibercept flattens the PED a bit better than ranibizumab, but there was no difference on final VA.[32] In HARBOR, patients who had complete flattening of PEDs actually had three times higher risk of geographic atrophy.[29] I also don't chase PEDs. If my patient gets better after I treat their fluid, I'm happy.

DR. DANZIG: I agree; the best corrected VA does not correspond to PED height. However, we also know that 50% of patients within a year will have visual decline or worsening of their neovascular component of their AMD if left untreated.[3] It's a balancing act. If I have patients with fluid or a small amount of hemorrhage on presentation and that resolves, I treat the PED because I know the fluid or hemorrhage is going to recur if I don't. Like Dr. Weng, I don't completely flatten it. I also tolerate some level of PED if it fluctuates a bit, and I do try to keep these patients on a somewhat regular treatment interval. It's about finding the right interval and right medication for each patient.

Q | DR. KHANANI: How do you manage your patients with persistent fluid? Does the type of fluid impact your management strategy?

DR. SINGER: I treat them the same in the early stages. If I'm in the first 3 to 6 months, I'm going after everything. As time progresses, I still treat IRF as aggressively as I can. If I'm unable to dry out the patient after three or four injections, I will switch drugs. I'll try to choose the strongest drug with the smallest interval to give it the best chance of drying. I'll only begin to extend the interval with some fluid after I've treated the patient over and over with the same response.

I do check VA and OCT scans very carefully. If there's no change, I'll increase the interval from 4 weeks to 6 weeks to 8 weeks. I'll go as long as 12 weeks in some patients. However, if VA begins to change from the patient's standpoint or objectively from the OCT, or on clinical exam, I'll contract the interval by at least 2 weeks.

DR. KHANANI: What are your criteria for switching a patient from one agent to another, and how long do you treat with the first agent before you switch?

DR. WENG: I usually wait to see how they do after five or six injections. If they still have persistent fluid after receiving that many injections in a row at a 4-week interval, I'll consider switching. In patients like this, I also like to pause and rethink my diagnosis, remembering that there are many mimickers, like polypoidal choroidal vasculopathy (PCV), that resemble neovascular AMD, but respond better to other types of therapy. Additional testing such as FA or indocyanine green (ICG) chorioangiography can be valuable in confirming the correct diagnosis.[33]

DR. KHANANI: I agree. I usually repeat FA and ICG chorioangiography after 6 months of monthly treatment and no improvement.

Many of us are moving away from taking FA and ICG at baseline, but these tests can help diagnose conditions like PCV in the future because you can compare imaging from different timepoints and see if there is a difference in exudation or leakage. It's very smart to use multimodal imaging. OCTA is another technology that most of us are using.[34] It hasn't found the perfect space because it's time consuming, but using a combination of imaging modalities is a good idea when you're switching a patient from one drug to another.

DR. DANZIG: I have OCTA in my practice, and I order it semi-regularly, especially in patients who can't tolerate fluorescein. OCTA is noninvasive and faster than getting an FA for these patients. Interpreting the OCTA is an issue. Does the treatment depend on the OCTA? How often should we be getting OCTA? We're still determining the answers to these questions, but I do think there is value in it.

DR. KHANANI: OCTA helps me determine if there's choroidal neovascularization (CNV), especially when there's some elevation indicating fluid on the OCT, but you see no significant leaks on the FA. I get an OCTA in all new patients. That said, it can be time-consuming and difficult to do every single visit.

NEW TREATMENT APPROACHES FOR AMD MANAGEMENT

Brolucizumab

Q | **DR. KHANANI**: Brolucizumab received US FDA approval in October 2019 based on the pivotal HAWK-HARRIER study, which showed that it dried the retina better than aflibercept.[35] In those trials, 1,817 patients with untreated, active CNV from AMD were randomized to either 3 or 6 mg of intravitreal brolucizumab or 2 mg aflibercept. After 3 monthly loading injections, the brolucizumab cohort received injections at a 12-week interval but were adjusted to 8-week intervals if disease returned. Patients in the aflibercept cohort were dosed every 8 weeks. After 48 weeks, brolucizumab was noninferior to aflibercept in visual function and more than 50% of eyes treated with brolucizumab 6 mg were able to maintain 12-week dosing.[35]

What is your experience so far with brolucizumab, and how are you using in your practice?

DR. DANZIG: I was pretty enthusiastic about incorporating brolucizumab into my practice, and I have numerous patients who have done quite well on it. There is an ongoing investigation regarding the incidents of inflammation, vasculitis, and retinal arterial occlusion after administration of brolucizumab, and that has caused some worry across the retina community.[35,36] The incidence is quite low, less than 1 in 1,000. Patients who have done well, often continue to do very well. However, patients who have had an adverse event may have suffered irreversible vision loss, which is quite scary.

I think the key in today's world is to have a very honest, frank discussion with patients stating that there's an outside chance they could have some inflammation and vision loss. However, without treatment they may also have vision loss.

DR. KHANANI: I have used brolucizumab and have personally had no cases of retinal artery occlusion. However, we just published two cases in *American Journal of Ophthalmology Case Reports* detailing artery occlusion and vasculitis.[36,37] No one will argue efficacy; brolucizumab is the most potent drying agent compared to aflibercept or ranibizumab. Safety is a concern and needs to be a patient-level discussion of the potential risks and benefits.

Port-Delivery System with Ranibizumab

Q | **DR. KHANANI:** The port-delivery system with ranibizumab is a permanent drug reservoir that's implanted surgically through a 3.5-mm scleral incision in the pars plana. It is designed for sustained delivery of ranibizumab via passive diffusion. The port-delivery system is refilled in the office setting using a specialized needle for the refill-exchange procedure.

Dr. Singer, you are an investigator in the port-delivery system, and you've participated in the LADDER, ARCHWAY (NCT03677934), and PORTAL extension (NCT03683251) studies.[38,39] We now have end study data from LADDER that shows the high-dose 100 mg/mL group had a median time to refill of 15.8 months after surgery. What are your thoughts on the port-delivery system, and what do you think of the data so far?

DR. SINGER: LADDER and ARCHWAY are game changers. In the LADDER study, more than 80% of patients were able to make it past 6 months, with the median time over a year, without a refill.[38,39] My patients are ecstatic; they love the concept. It is a surgical procedure, but most specialists are able to master it relatively easily. That said, the refill procedure is much more cumbersome than most specialists are used to. However, I think it's easily mastered, and the tradeoff is worth it.

Although the data have not been published, I am curious to see the rates of macular atrophy in patients who have the port-delivery system versus patients who receive monthly anti-VEGF injections. If you look at the geographic atrophy drugs currently studied, they're all trying to stop inflammation.[40] I personally believe that every time you inject something in the eye, you cause some type of microscopic inflammation.

I'm also involved in the PAGODA trial (NCT04108156), which is a port-delivery system for diabetic macular edema that is currently recruiting. I frame it for my patients as an insulin pump, and they all understand and are very excited. Going forward, there will be a percentage of my patients using it once approved because it may minimize many of the problems we've discussed: injection fatigue, loss to follow-up, and drug durability. Patients will end up with better quality vision. I'm a big proponent of it, and I think it will have a place in our armamentarium going forward.

DR. KHANANI: As an investigator in LADDER, ARCHWAY, PORTAL, and PAGODA, I've seen how patients behave when they come in for a port-delivery follow-up visit versus injection. They are less anxious because they know they're not receiving an injection. As physicians, sometimes we're too busy to appreciate the emotional

aspect and burden of monthly injections. The data from the ARCHWAY study will read out this year and if there's no difference and patients do equally well with the port delivery system versus monthly ranibizumab injections, then most of us will offer port delivery system as an option for our patients once it's approved.

The surgical points you mentioned are crucial; surgery will never be as safe as intravitreal injections but safety has improved considerably over time due to the learnings from the LADDER study. In the LADDER study, the vitreous hemorrhage rate was less than 5%, down from 50% after the procedure was optimized.[39] There are many factors that we need to pay attention to during the surgery to have a good outcome, including properly closing the conjunctiva without exposure of the implant, ensuring the wound is the correct size, and making sure adequate laser is done on the choroid before the port-delivery system is placed. This is all achievable with training. Sustained delivery is even more important during the COVID-19 pandemic when patients can't come in for their frequent clinic visits. If I had a patient with a port-delivery system and if they couldn't come in for their follow-up, I would be okay as I know that they're unlikely to lose their vision.

Faricimab

Q | **DR. KHANANI:** Faricimab is the first bispecific antibody designed for the eye and has the potential to be dosed every 4 months.[41-44] It blocks VEGF-A as well as ANG-2. The phase 2 STAIRWAY trial confirmed the safety and efficacy of faricimab in patients with neovascular AMD. The phase 3 TENAYA AND LUCERNE studies in neovascular AMD are under way (NCT03823287 and NCT03823300, respectively).[41] If the trial is positive, how do you see faricimab fitting into your clinical practice?

DR. WENG: Faricimab is a promising drug candidate. We need agents that not only last longer but also work better for our patients. I think faricimab has demonstrated potential to do both because it blocks both VEGF-A and Ang-2. Ang-2 is a molecule that destabilizes the Tie2 pathway, which is important for vascular stability. Our therapies need to go beyond VEGF-A.

I'm looking forward to seeing the data from TENAYA and LUCERNE. If the safety and efficacy data parallels what we've seen so far, this will be a great option for our patients.

Q | **DR. KHANANI:** I agree; going beyond VEGF-A may make a big difference in terms of long-term efficacy. We have to wait for the phase 3 trials, but I think there's a durability signal here in neovascular AMD. The BOULEVARD trial with faricimab in DME showed there was efficacy and durability as well.[45]

Why is blocking Ang-2 important? What did the STAIRWAY trial tell us about the efficacy and safety of faricimab? Were there any cases of retinal vasculitis or retinal artery occlusion?

DR. DANZIG: Ang-2 and VEGF-A synergistically drive vascular instability causing more inflammation, vascular leakage, and neovascularization. Therefore, we needed another molecule that can target our patients with vascular diseases like neovascular AMD, diabetic retinopathy, and retinal vein occlusion, because we need to better stabilize these patients visually and on a microvascular level.

STAIRWAY is a 52-week study that assessed two extended dosing regimens of faricimab 6.0 mg given every 12 to 16 weeks, compared to ranibizumab 0.5 mg every 4 weeks.[41,43,46]

There were three arms: faricimab every 12 weeks, faricimab every 16 weeks, and ranibizumab every 4 weeks. Patients received four loading doses. At week 24, patients in the 16-week faricimab arm were switched to 12-week dosing if they had active disease. At week 24, 65% of patients in the faricimab arms had no disease activity, and were eligible for q16-week dosing. Visual and anatomic improvements were comparable to the ranibizumab arm at the end of the 52-week study. Patients treated with faricimab every 16 weeks had a mean improvement of 11.4 letters from baseline, compared with 10.1 letters in patients treated with faricimab every 12 weeks, and 9.6 letters in patients treated with ranibizumab every 4 weeks.

Faricimab was well tolerated, and rates of ocular and systemic adverse events were similar to ranibizumab; no new safety signals were demonstrated. We're currently involved in phase 3 trials, TENAYA and LUCERNE, for neovascular AMD. Hopefully, faricimab will be confirmed efficacious and safe, and we can move forward with another promising medication for our patients.

OPT-302

DR. KHANANI: We'll have to determine what option is the best for specific patient phenotypes and how they can achieve maximum efficacy and durability. This is clearly an exciting time. In terms of different pathways, OPT-302 is a VEGF-C/D trap molecule that is designed to be used in combination with standard-of-care anti-VEGF-A therapies.[47] The phase 2 AMD data were very positive for OPT-302. We saw significant visual gains of monthly ranibizumab plus OPT-302 compared to monthly ranibizumab in 366 patients.[48,49] They had two different doses of OPT-302 (0.5 mg and 2.0 mg), and the higher dose performed better.

This gives additional options for patients with persistent fluid or decreased vision that maybe we need to block VEGF-C and VEGF-D on top of VEGF-A to get better outcomes. Phase 3 planning is underway.

GB-102

Q | **DR. KHANANI:** Dr. Singer, you are currently involved with the GB-102 trial. That trial is fully recruited, and we are awaiting the data. Tell us a little bit about the technology and how it will be able to address the unmet need of durability.

DR. SINGER: GB-102 is an intravitreal injectable depot formulation of sunitinib malate, a tyrosine kinase inhibitor that blocks multiple angiogenesis pathways.[50] The original phase 1 trial showed sustained drug levels in the retinal tissue through 6 months following a single injection.[51]

The downside is that the medicine had migration issues. The medicine would migrate not only within the posterior chamber, but into the anterior chamber. The phase 2 trials were temporarily suspended because of migration issues running forward. When it worked,

patients didn't need rescue therapy. However, the molecule has to stay in place to be effective and safe.

DR. KHANANI: I agree. To be considered, all new agents need to have both better durability and similar safety profile compared to the currently approved agents. GB-102 was optimized to reduce particle dispersion in the macular edema study in patients with DME/RVO as well as the ALTISSIMO study in patients with neovascular AMD, but there were patients in these studies, especially the high dose 2-mg group, who still had some dispersion. Therefore, the studies were put on hold and it was decided to not use the 2-mg dose in the clinical trials.[52]

KSI-301

DR. KHANANI: KSI-301, a novel anti-VEGF antibody biopolymer conjugate, is a large molecule that is injected in the vitreous and is designed to have better durability compared to currently approved agents.[47] I've been involved with both the phase 1b and DAZZLE (NCT04049266) trials.[53] The phase 1b trial has recruited 130 patients randomly assigned to KSI-301 2.5 mg or 5 mg. Patients initially received three injections of KSI-301 4 weeks apart. They were assessed for retreatment beginning at week 16.

We have seen some promising early data from the phase 1b trial.[53] AMD patients are going much longer between injections than what we have seen with other agents, with the majority going more than 12 weeks and up to 24 weeks. I think there's potential to decrease treatment burden due to the durability of KSI-301 based on the molecular design. The safety profile has also been good so far. What is your overall impression of KSI-301?

DR. DANZIG: My impression has been quite positive. We're moving the ball forward. We had 12-week dosing in the HAWK and HARRIER trials; we have the TENAYA and LUCERNE phase 3 trials up to 16 weeks, and the phase 2 DAZZLE trial has patients going 20 weeks after loading doses. In DAZZLE, the interval can decrease to less than 20 weeks if they show disease activity. Phase 1b data, so far, indicate that some patients are able to go that distance. This all goes back to the theme of personalized treatment, finding the molecule that works best for a particular patient. We've only seen data from a limited number of patients, but the safety so far seems excellent. There has been no inflammation or infection in the early data. You worry about glaucoma because it's a bigger molecule and the volume injected is 100 µl. That's not proven to be the case though. Hopefully, it will continue to be safe and effective moving forward.

GENE THERAPY FOR AMD

Q | **DR. KHANANI:** RGX-314 is a gene therapy currently in development.[47,54-56] It's a one-time subretinal treatment for neovascular AMD that includes the NAV AAV8 vector containing a gene encoding for a monoclonal antibody fragment, which blocks VEGF activity, preventing the development of leaky blood vessels and accumulation of retinal fluid. RGX-314 is delivered through subretinal surgery in the operating room and has shown positive data. Trials are being designed to deliver it in clinic using suprachoroidal delivery to determine if it's effective. The data from the surgical trial program has been positive in terms of protein production and decreased need for rescue injections among their five cohorts.[54]

ADVM-022 is an intravitreal gene therapy designed for long-term aflibercept expression following a single in-office intravitreal injection.[57,58] I recently presented the data at the 2020 ARVO (virtual) meeting. The data showed that all neovascular AMD patients in the high-dose group have gone 1 year or longer without need for rescue.[59] These were heavily pretreated patients with an average of around nine injections in the prior 12 months. What are your thoughts on the potential of these therapies?

DR. WENG: Gene therapy was once thought to only be applicable to rare inherited retinal dystrophies. It's very promising that we can now translate the concept of gene therapy and apply it to one of our most common diseases, neovascular AMD.

Rather than targeting a specific mutation in a monogenic disorder, gene therapy in neovascular AMD works by turning the body into a biofactory so that the patient's cells can produce their own anti-VEGF. Two leading candidates in this space are RGX-314 and ADVM-022. RGX-314 is a novel AAV-8-based subretinal gene therapy that is delivered with a concurrent pars plana vitrectomy. RGX-314 has been assessed in a phase 1, dose-escalation trial of 42 patients.[47,54,55] In cohort five, the group that received the highest dosage of gene therapy, patients not only demonstrated positive visual and anatomic responses, but nearly three-quarters remained injection-free up to 9 months following their gene therapy treatment. There have been a small number of procedure-related serious adverse events, including endophthalmitis and retinal detachment, so of course the potential risks of surgery should be considered. That said, the prospect of a single-dose treatment is exciting. Investigators are also examining a suprachoroidal route of delivery for RGX-314, which might allow us to move this type of therapy out of the operating room and into the office, thereby avoiding a vitrectomy and the implications of taking elderly patients to surgery.

ADVM-022 utilizes an AAV2 vector. However, it's not the conventional AAV2 vector that has been tried in the past and associated with some of the earlier failures in neovascular AMD gene therapy. The ADVM-022 product uses AAV.7m8, a designer vector capsid carrying an aflibercept-coding sequence; this proprietary capsid allows the product to penetrate through the internal limiting membrane even though it's injected intravitreally. This delivery route is advantageous because we're all very familiar with intravitreal injections, and they generally have an excellent safety profile. Thus far, there is data available from twenty-one patients in three cohorts.[47,57,58,60] All patients in the high-dose cohort 1 have remained injection-free, some for more than a year. The durability implications of a potential "one-and-done" treatment are significant.

DR. KHANANI: We may be able to achieve better VA outcomes with gene therapy because, just like port delivery, there's sustained delivery. If

you look at the protein data from RGX-314, the level achieved is as good as continuous ranibizumab. Preclinical data from ADVM-022 shows the level is just as good in nonhuman primates as monthly aflibercept. Sustained delivery is a game changer. I think gene therapy will be the next step where we will see the long-term benefit of sustained delivery.

It's also important to note that ADVM-022 and RGX-314 are being tested in previously treated patients. As I stated earlier, patients in ADVM-022 cohort 1 had a mean of nine injections in 12 months prior to receiving ADVM-022. It's amazing that patients who were receiving injections every 4 to 6 weeks prior to going in the trial have received no injections at 1 year or longer and have stable OCTs. Long-term safety needs to be proven, but these are exciting developments.

How do you plan to incorporate the delivery of these new agents into your practice once they're available?

DR. SINGER: I still believe we are going to give initial injections because I want to see how patients respond. I think the port-delivery system with ranibizumab is great for maintenance, but we won't begin treating patients with it. If the patient responds to the injections, wants longer durability, and they are a good candidate for surgery, port delivery fits right into the treatment paradigm.

I can see myself using faricimab for lesions that aren't responsive to pure anti-VEGF. Instead of switching from agent A to agent B, I am going to bring faricimab into the fold because it's multimodal therapy. Gene therapy is very attractive because you treat the patient once, but we need more information about the risks.

DR. DANZIG: I agree that intravitreal injections are the way to go at first. As we move forward into the future, if a patient cannot keep up with his or her set frequency of injections, we can offer the PDS or gene therapy—something that will give them longer durability and the outcomes they want. It's an exciting time to be a retina specialist, and our patients are blessed to have these new and evolving options.

CASE STUDIES

CASE 1: Persistent SRF

DR. DANZIG: Our first case is of a 79-year-old female with persistent SRF. She was diagnosed with wet AMD in November 2014. I tried to enroll her in the MERLIN trial, but she developed a hemorrhagic PED. She was receiving monthly injections, and still had 20/30 vision even with fluid. In November 2019, she had a little PED and SRF (Figure 1). I injected her with brolucizumab in November and December, and her fluid resolved.

I saw her in January 2020 for a third brolucizumab injection, and the PED height decreased, fluid remained resolved, and her vision was maintained at about 20/25 to 20/30 (Figure 2). Seven weeks later, her vision dropped to 20/100. There was no evidence of an inflammation or artery occlusion. We just couldn't get her to an 8-week interval (Figure 3). We injected aflibercept, for the brolucizumab label does not allow treatment sooner than 8 weeks following the initial three monthly loading doses. Fortunately for this patient, her vision improved to 20/40.

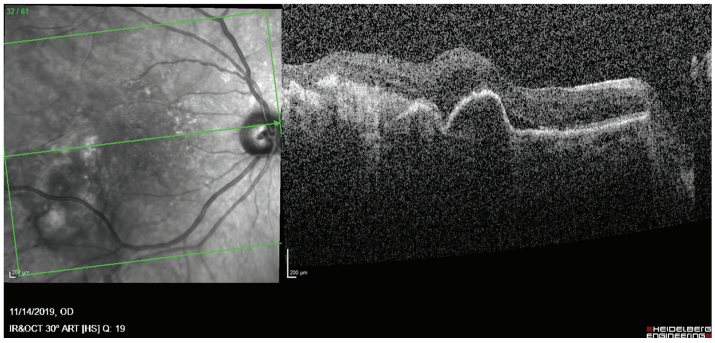

Figure 1. Case 1: A 79-year-old female with persistent SRF on monthly injections.

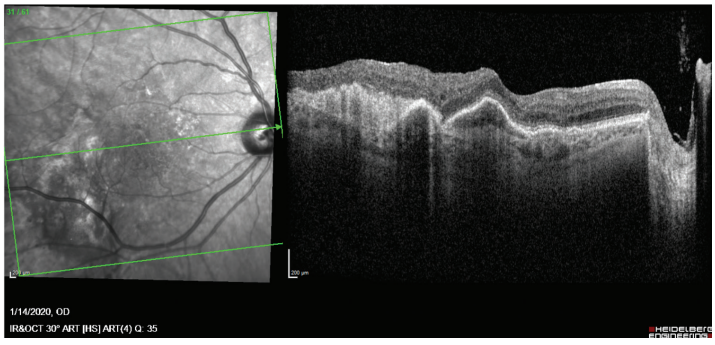

Figure 2. Case 1: A 79-year-old female with persistent fluid after third brolucizumab injection.

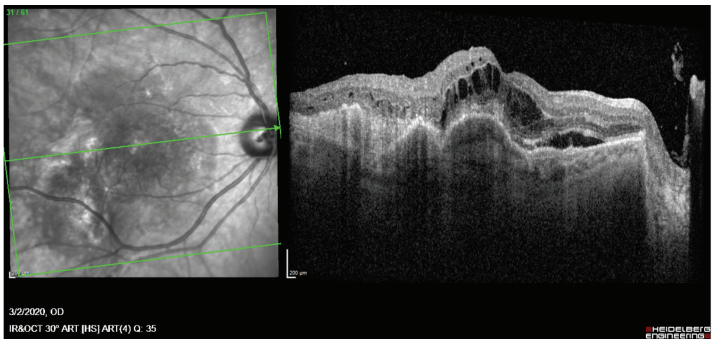

Figure 3. Case 1: Seven weeks after third brolucizumab injection.

DR. SINGER: In my experience, I have seen that usually newer anti-VEGF medications are either stronger or longer but rarely both. Usually when treating intractable fluid, the new medicine is able to dry out the retina but is not able to extend the dosing interval. I initially observed this when switching form ranibizumab to aflibercept and it seems to be true from aflibercept to brolucizumab.

DR. WENG: As I alluded to earlier, there is tremendous variability in response among different patients. While some patients can be maintained successfully on every-8-week treatment, others being treated with the exact same drug may require monthly injections, even if their clinical findings are similar. There is ample opportunity in this space to learn how we can better personalize treatment approaches for our patients. Elucidating genetic drivers, imaging biomarkers, and clinical characteristics will further our understanding of this complex disease.

DR. KHANANI: This case highlights the unmet need of agents that have good durability. You used brolucizumab, which dries the retina better than aflibercept, but you couldn't get the patient past 6 weeks without fluid recurrence. The new molecules and PDS will help address this problem of persistent activity with frequent injection.

CASE 2: New PED Onset

DR. SINGER: Our next case is a 77-year-old female with 20/25 vision, a drusen, and RPE changes consistent with dry AMD in February 2015. One month later she returns and notices changes on her grid in her right eye. Her vision is 20/100. Her fundus is noted to have a new PED with edema.

We started her on monthly aflibercept (Figure 4). The IRF resolves, and we flatten her PED. However, the PED returns and fluid becomes more recalcitrant when we try to extend the interval to 6 weeks. She is then injected with aflibercept monthly over the next 4 years but still has persistent retinal edema. Her vision ranges from 20/70 to 20/30, depending on the year.

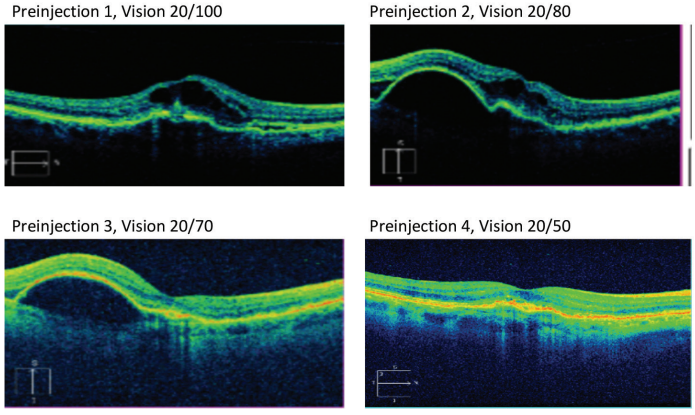

Figure 4. Case 2: A 77-year-old female with dry AMD on monthly aflibercept.

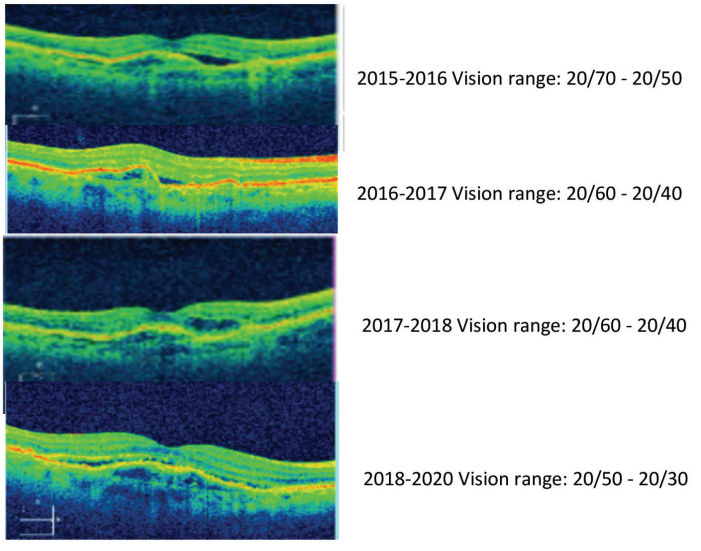

Figure 5. Case 2: A cross-section of an average scan in a given year for a 77-year-old female with dry AMD.

Figure 5 shows the cross-section of an average scan in a given year. Her PED is flatter with the higher frequency anti-VEGF dose, but she still has little bits of fluid that hamper her vision. I put her on brolucizumab in February 2020, and we were finally able to dry up the fluid. The PED flattened further and her vision improved. So far, she looks good. This is a great example for converting to brolucizumab because obviously monthly aflibercept wasn't strong enough.

DR. DANZIG: This is an excellent case focusing on the theme of effectiveness and durability in the real world. This type of patient is unusual, not because of her pathology, but because of her amazing

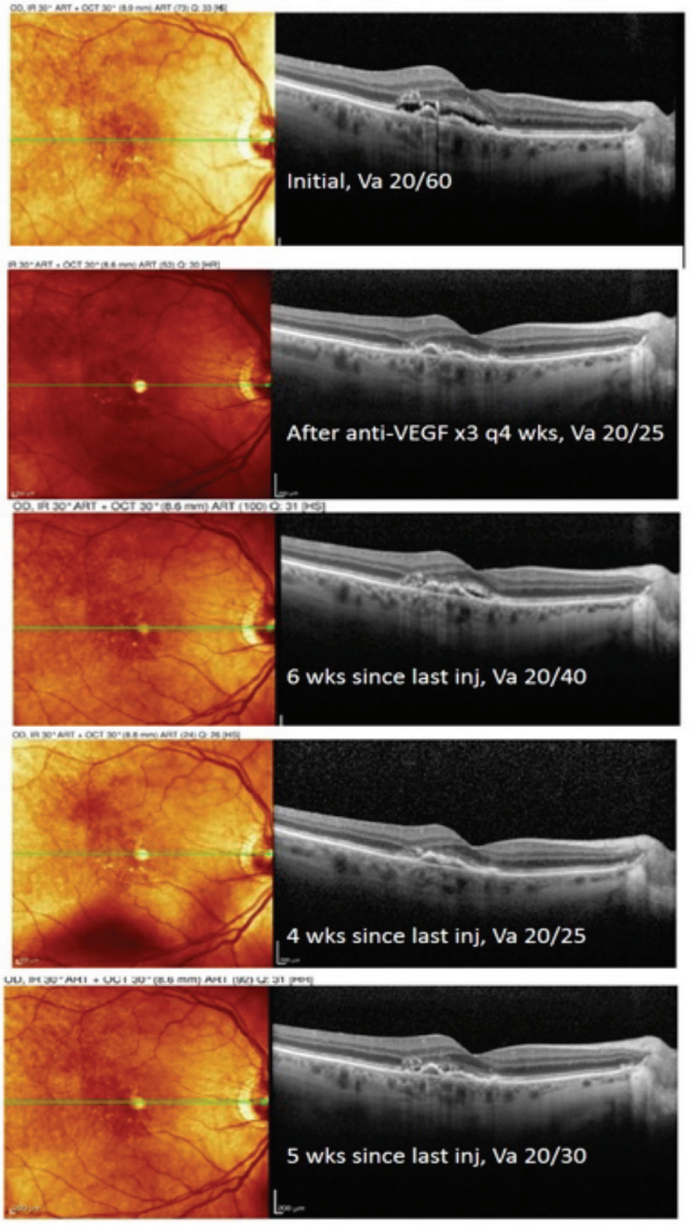

Figure 6. Case 3: A 74-year-old female with neovascular AMD.

ability and willingness to maintain compliance with q4-6 week appointments over 4 years! However, it is unrealistic to expect many patients to adhere to this regimen. With promising new medications and surgical options in various phases of clinical trials, the future is promising for patients like Dr. Singer's to be able to maintain good vision with prolonged durability.

DR. WENG: Dr. Singer's case demonstrates one of the benefits of having more treatment options available for our patients. While we have yet to fully understand why certain patients respond well to one drug but not another, we all have patients for which this is true. With several other promising agents in the drug pipeline—such as abicipar and faricimab—our armamentarium of drug choices will continue to grow, and our patients will certainly benefit.

DR. KHANANI: This case really highlights that persistent fluid causes vision to change even with maximum aflibercept. There is clearly a need for additional pathways like Ang-2 inhibition with faricimab or VEGF-C and VEGF-D inhibition with OPT-302 that may allow us to control this patient. Port delivery could extend the treatment interval for this patient also where you're refilling the port much less often than you're giving injections. Another approach in the future could be gene therapy, to allow sustained expression of anti-VEGF to control exudation.

CASE 3: Returning Fluid and Vision Decline

DR. WENG: Our next case is a 74-year-old female with neovascular AMD. When she first came to me, she had evidence of exudation and her vision was 20/40. After three anti-VEGF loading doses, she was completely dry and her vision improved to 20/25. I started extending in 2-week increments. At 6 weeks, her fluid recurred and her vision dropped to 20/40. I reverted the interval back to every 4 weeks. Her fluid resorbed and her vision again improved to 20/25 (Figure 6). I tried extending her to 5 weeks, but you can see that when she returned, there was a hint of recurrent SRF. This is a patient who requires sustained monthly treatment and will be a great candidate for longer-acting agents.

DR. DANZIG: I agree, Dr. Weng, that a more durable agent is needed. Of note, she does have excellent vision and our goal will be to maintain that excellent vision in the safest way possible. Early data from various clinical trials, including gene therapy, along with port-delivery system, are encouraging in terms of safety.

DR. SINGER: This patient is a good candidate for extended release medications or port-delivery system or gene therapy as they have a higher burden of injections in order to maintain vision.

DR. KHANANI: I agree. A decrease in treatment burden is a big issue here, and this case highlights the relationship between vision and fluid. Once approved, sustained delivery, through port delivery or gene therapy, will help this patient considerably.

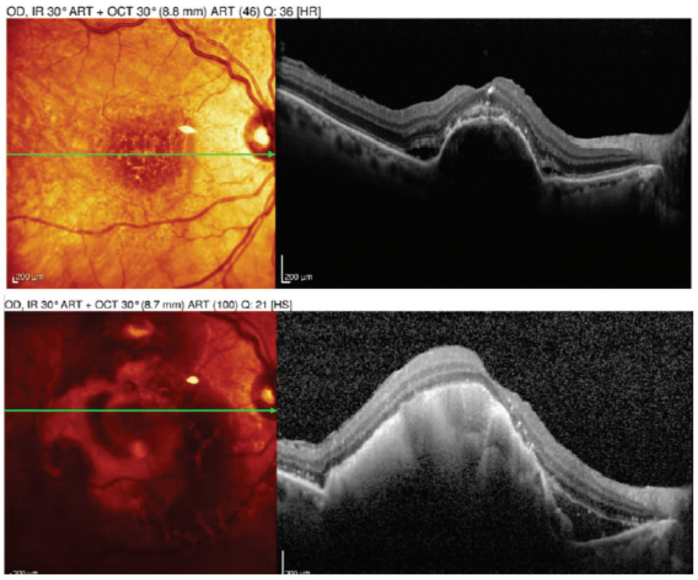

Figure 7. Case 4: An 83-year-old female with neovascular AMD and a large PED.

CASE 4: Treatment Burden and Missed Visits

DR. WENG: Our final case is an 83-year-old widowed female with neovascular AMD and a large PED who was improving on monthly anti-VEGF (Figure 7). After receiving seven injections, her vision improved to 20/25. Her treatment burden, however, was significant. A clinic visit was a 4-hour roundtrip ordeal, and she had to be accompanied by a neighbor or a friend each time. Because monthly injections were incredibly burdensome, she stopped coming.

She did not show up for her next monthly injection until 10 weeks later. By that time, she had developed a massive subretinal hemorrhage with a possible RPE tear. Unfortunately, her vision dropped to counting fingers at 2 feet.

This is an example of a patient who really suffered from injection burnout. Tragically, even though she was responding well, she didn't return as directed and now has irreversible vision loss. Patients often believe they can simply pick back up on injections and restore their vision to what it was previously. Unfortunately, that's not always the case. With longer acting therapies in the pipeline, hopefully we can ameliorate these compliance issues and prevent things like this from happening in the future.

DR. DANZIG: This is a very unfortunate, real-world outcome, one which we all see in our respective clinics. Even though brolucizumab would have been a great option, I still would have liked to have seen this patient on a monthly basis for probably 6 to 8 months, simply to ensure absence of any adverse event. Perhaps this type of patient would benefit most from port delivery system.

DR. SINGER: This patient could benefit from medications with increased duration of effect. Using brolucizumab, faricimab, abicipar, port delivery system, or gene therapy might decrease her need for follow-up visits and enhance her compliance.

DR. KHANANI: This case goes to our initial discussion of real-world outcomes and injection burden. It clearly highlights that there are patients who don't come to the clinic and have irreversible vision loss, and illustrates why real-world outcomes differ from clinical trials.

Thank you to our panel for your thought-provoking comments on the latest advances in the treatment of AMD. ■

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THE AMD TREATMENT BURDEN: CURRENT STATUS AND PROMISING SOLUTIONS

Release Date: July 2020
Expiration Date: August 2021

INSTRUCTIONS FOR CREDIT

To receive *AMA PRA Category 1 Credit™* for this activity, you must complete the Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form. To answer these questions online and receive real-time results, please visit http://evolvemeded.com/online-courses/2008-supplement1. Upon completing the activity and self-assessment test, you may print out a CME certificate awarding 1 *AMA PRA Category 1 Credit™*. Alternatively, please complete Pretest/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. If you experience problems with the online test, please email info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your valid 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
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 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
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Decribe the differences in real-world clinical outcomes with those from prospective clinical trials.	_____	_____	_____
Develop individualized treatment regimens for patients with AMD who may benefit from treatments with longer duration.	_____	_____	_____
Discuss newer compounds in development or recently approved compounds that are designed to improve visual outcomes while decreasing treatment burden.	_____	_____	_____

POSTTEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation

1. Based on this activity, please rate your confidence in your ability to manage patients with AMD (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. Based on this activity, please rate how often you intend to apply the latest treatments in AMD (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. Typically, the biggest cited unmet need in the treatment of wet AMD is _____.

a. Agents at a lower cost
b. Personalization
c. Remote monitoring of fluid levels
d. Drug durability

4. A 76-year-old female with wet AMD has received monthly injections with aflibercept for the past year. She travels 3 hours roundtrip with a caretaker for her appointments and has indicated this might be difficult for her caretaker to maintain. Her vision is 20/40 and stable. She has persistent subretinal fluid that has not resolved. Which of the following may offer her the same quality of treatment but reduce the treatment burden?

a. Switch to brolucizumab
b. Nothing; the subretinal fluid is not impacting her vision yet, so monthly injections are still needed.
c. Recommend gene therapy
d. Order fluorescein angiogram and indocyanine green chorioangiography at her next appointment, because it could be a misdiagnosis.

5. What is the recommended first-line treatment for an 80-year-old male with a high PED and associated intraretinal fluid?

a. Generic bevacizumab
b. A branded anti-VEGF
c. Laser photocoagulation
d. Intravitreal corticosteroids

6. A 75-year-old female has a small amount of hemorrhage with a PED. Do you need to completely flatten the PED during treatment?

a. No. There is a possible risk of geographic atrophy with PED flattening.
b. Yes. The patient will achieve a higher BCVA if the PED is flattened.
c. No. The patient will lose vision if the PED is flattened.
d. Yes. There is no risk for geographic atrophy if the PED is flattened.

7. Brolucizumab is under ongoing investigation for safety because of what associated adverse event?

a. Inflammation
b. Glaucoma
c. Retinal Arterial occlusion and Occlusive Vasculitis
d. Retinal detachment

8. A 70-year-old female patient with wet AMD and no significant comorbidities has had a good response to quarterly ranibizumab for the last 18 months. Her vision is 20/30. She is starting to ask how many more injections are needed and seems interested in fewer appointments. All but which are potential options to consider?

a. Switch to aflibercept
b. Switch to brolucizumab
c. Stay with quarterly injections of ranibizumab and stress the importance of compliance
d. All of the above

9. What are the potential barriers to the gene therapy RGX-314? *Select all that apply.*

a. It requires a vitrectomy in the operating room
b. Drug durability isn't long enough
c. Learning curve for physicians
d. Poor efficacy

10. In what clinical scenario is some subretinal fluid acceptable?

a. Subretinal fluid is never a concern and can protect vision in some patients.
b. Only after three loading doses is subretinal fluid acceptable; beyond that it must be treated aggressively.
c. In patients with good, stable vision after maximum therapy a small amount of fluid is acceptable.
d. Subretinal fluid should always be treated aggressively.

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

I plan to make changes to my practice based on this activity. _____ 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

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.

_____