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MODERNIZING MEDICAL RETINA: REVIEW OF THE PIPELINE



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Modernizing Medical Retina: Review of the Pipeline

CONTENT SOURCE

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

ACTIVITY DESCRIPTION

This supplement summarizes an in-depth discussion into the available options for treatment of retinal diseases and the challenges faced by retina specialists in the current environment of COVID-19, in addition to patient compliance with demanding regimens. The faculty also reviews therapies under investigation for these conditions and the potential they have for longer duration and improved outcomes.

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 pros and cons of current therapy options for wet age-related macular degeneration.
- **Articulate** the challenges facing retina specialists related to the complexities of managing patients with wet age-related macular degeneration.
- **Assess** pipeline candidates under investigation for this patient population.

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DIGITAL EDITION

This supplement is part of a larger curriculum. To view all activities in the curriculum, go to <https://evolvemeded.com/course-group/modernizing-medical-retina-review-of-the-pipeline>.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/
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1. Please rate your confidence in your ability to assess pipeline candidates under investigation for patients with diabetic retinopathy (DR, diabetic macular edema (DME, and wet age-related macular degeneration (AMD) (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
2. A 66-year-old man with wet AMD and 20/40 vision cannot extend beyond 8 weeks with ranibizumab. He has been adherent to therapy but is starting to complain about the injection burden. What novel therapy may be appropriate (if approved)?
 - a. Faricimab
 - b. Gene therapy
 - c. Port delivery system (PDS) with ranibizumab
 - d. All of the above
3. According to pivotal clinical trials, what treatment schedule will achieve the best gains in visual acuity for patients with wet AMD?
 - a. Monthly
 - b. Treat-and-extend
 - c. As-needed (prn)
 - d. There is no difference in visual acuity gains between treatment schedules
4. Which is TRUE regarding studies comparing treat-and-extend versus other regimens?
 - a. Treat-and-extend regimens lead to significantly inferior visual outcomes compared to monthly.
 - b. In most studies, treat-and-extend reduces the visit/injection burden by approximately 50% compared to monthly.
 - c. Treat-and-extend regimens reduce the visit/injection burden without significantly compromising visual acuity outcomes in comparison to prn or monthly regimens.
 - d. Treat-and-extend regimens lead to inferior visual outcomes compared to prn regimens.
5. Approximately _____ of patients with wet AMD who are receiving anti-VEGF injections are lost to follow-up in the first year of treatment.
 - a. 14%
 - b. 22%
 - c. 36%
 - d. 52%
6. A 72-year-old White female with coronary artery disease, glaucoma, and obesity continues to have persistent subretinal fluid with monthly injections of aflibercept. She previously had suboptimal responses with bevacizumab and ranibizumab. The fluid has improved with aflibercept but has not resolved. She relies on her daughter for transportation to and from appointments, and the treatment burden on the family is substantial. Assuming that faricimab is FDA-approved, which statement might you use to counsel her in potentially switching agents?
 - a. Faricimab is injected into the suprachoroidal space and offers a durability of 6 months.
 - b. In the phase 3 TENAYA and LUCERNE studies, nearly 80% of wet AMD patients were able to achieve a q16-week interval.
 - c. Faricimab is a bispecific molecule that targets VEGF-A, but also targets Ang-2 which may help increase vascular stability.
 - d. Faricimab could potentially offer better efficacy and durability, but patients had significantly higher rates of retinal vasculitis in the phase 2 and phase 3 studies.
7. Which of the descriptions represents the most ideal patient for the PDS with ranibizumab?
 - a. A treatment-naïve patient with many systemic comorbidities and a history of glaucoma.
 - b. A patient who is doing well on anti-VEGF treatment but fearful of injections and has expressed interest in fewer visits and/or injections.
 - c. A patient who is doing well on quarterly injections of anti-VEGF with no significant socioeconomic challenges.
 - d. A patient who has demonstrated a suboptimal response to ranibizumab in the past, but whose disease activity is well controlled on aflibercept every 10 weeks.
8. ADVM-022 and RGX-314 are gene therapies that use _____ to carry a gene into the nucleus of cells.
 - a. A viral vector
 - b. A nonviral vector
 - c. DNA
 - d. Cell therapy
9. In the LADDER phase 2 study of PDS, the median time to refill in the highest-dose arm was _____.
 - a. 6 months
 - b. 9 months
 - c. 12 months
 - d. 15 months
10. Which statement best describes OPT-302?
 - a. OPT-302 is a coformulation drug that blocks VEGF-A and VEGF-C/D.
 - b. OPT-302 is a tyrosine kinase inhibitor that provides pan-VEGF blockade.
 - c. In a phase 2b study, OPT-302 used in combination with ranibizumab lead to superior visual acuity outcomes at 24 weeks in wet AMD patients compared to ranibizumab monotherapy.
 - d. OPT-302 is now being studied in two phase 3 studies that will compare visual outcomes of OPT-302 used in combination with ranibizumab/aflibercept versus OPT-302 monotherapy.

Modernizing Medical Retina: Review of the Pipeline

Advanced age-related macular degeneration (AMD) is a leading cause of irreversible blindness and visual impairment around the world. As many as 200 million people worldwide have some form of AMD. Because of our aging population, its prevalence is expected to grow rapidly during the next 20 to 30 years, reaching 300 million by 2040. Although the risk is low in younger and middle-aged individuals, adults aged 75 and older have a 25% risk of early AMD and an 8% risk of late AMD. Advanced AMD patients include those with geographic atrophy or neovascular AMD, the latter which affects about 17 million people worldwide.¹ There's a silver lining, however: neovascular AMD used to be a blinding disease. During the past 2 decades, very effective therapies have been developed to preserve and even improve vision in these patients. However, many challenges remain. The following roundtable convenes experts in retina to discuss optimal use of our current treatments as well as exciting agents in the pipeline.

— Christina Y. Weng, MD, MBA, Moderator

THE FUNDAMENTALS OF WET AMD

Q | Dr. Weng: The current standard of care for neovascular AMD is anti-VEGF in the form of intravitreal injections. We now have four agents, the most recently approved being brodalumab. When we talk about how we use these agents, many of us follow one of three different treatment schedules. According to the 2017 American Society of Retinal Specialists Preferences and Trends survey, 71% of retinal specialists in the United States use a treat-and-extend approach, 10% treat on a *pro re nata* (prn; as needed) basis, and 2% treat monthly.^{2,3} Let's imagine a new wet AMD patient walks into your clinic. How do you approach care? What agent do you begin with and why?

Basil K. Williams Jr, MD: In this situation, I'd get a feel for the patient's comfort with the diagnosis, the idea of getting injections, and the expected treatment length. I'd also assess their independence and ability to come to appointments. In general, due to insurance reasons, I initiate treatment with bevacizumab and use a treat-and-extend approach. I administer injections until the intraretinal fluid has resolved. At that time, I will gradually extend the injection schedule, most often 2 weeks at a time.

Dr. Weng: Our current anti-VEGF agents have a heavy treatment burden, which affects outcomes. Patients may not have transportation or accompaniment. Does that guide your schedule choice?

Dr. Williams: Their socioeconomic status does make a difference in my drug choice. If I have concerns about their financial resources, access, or transportation, I'll often start with aflibercept and try to extend the treatment for a bit longer. It also changes how I gauge the conversation. I tend to be more encouraging about the importance of injections, which is obviously something you have to reiterate with every patient. But I drive home this

point to a greater extent, because I know it may be challenging for them to return to the office.

Diana Do, MD: My approach is very similar. It's also important to confirm the diagnosis because there are masquerading syndromes that can mimic wet AMD (chronic central serous chorioretinopathy, polypoidal disease, adult-onset foveomacular vitelliform dystrophy, macular telangiectasia, acquired vitelliform maculopathy, basal laminar drusen, and acute exudative polymorphous vitelliform maculopathy).⁴ I complement my clinical exam with a host of imaging studies, including optical coherence tomography (OCT) and fluorescein angiogram (FA) if they are treatment-naïve. This helps me determine if the lesion truly is choroidal neovascularization (CNV). It also gives me a baseline to evaluate the lesion size and how it might respond to therapy.

I use a treat-and-extend regimen. I prefer to use on-label medicines such as ranibizumab or aflibercept, but in some cases, insurance companies require step-therapy, starting with off-label bevacizumab.

Dr. Weng: Is your preference for on-label medications, US FDA-approved medications, a safety or medicolegal reason? Or do you find the efficacy data more convincing in comparison to off-label bevacizumab?

Dr. Do: There's some element of both safety and efficacy. We've seen in other diseases, specifically diabetic macular edema, that there are differences among bevacizumab, ranibizumab, and aflibercept. Do these differences translate to wet AMD? Not always. However, many retinal specialists, including myself, feel that on-label drugs have been tested rigorously and some of them, especially aflibercept, can be extended longer than bevacizumab or ranibizumab. There are subtle differences, which is why physicians like having choices.

Peter Campochiaro, MD: I agree with this approach, and



"I think treat-and-extend is effective in the vast majority of patients. However, if a patient has poor vision in one eye and presents with neovascular AMD in the other eye, I am more aggressive and treat those patients monthly."

—Peter Campochiaro, MD

I think treat-and-extend is effective in the vast majority of patients. However, if a patient has poor vision in one eye and presents with neovascular AMD in the other eye, I am more aggressive and treat those patients monthly. Although only 2% of retinal specialists treat monthly, it is necessary in certain circumstances to give the patient the best chance of maintaining good vision.

Q | Dr. Weng: If you look at our major trials—ANCHOR and MARINA, CATT, VIEW I and VIEW II—monthly treatment provides the patient with the best visual acuity gains.⁵⁻⁸ I agree there are certain circumstances, such as a monocular patient, where you may want to consider monthly treatment, even though this treatment schedule is used less commonly by US retinal specialists.

Dr. Do mentioned that she will sometimes obtain FA, which is an endangered species nowadays. We don't order FAs as much as perhaps we should. Who uses FA and in what specific situations?

Dr. Campochiaro: I like to obtain an FA when I first see a patient to confirm the diagnosis and get a baseline. I then follow-up with periodic angiogram, maybe once a year, to assess treatment efficacy. FA doesn't influence the way I treat or the drug I use. All our anti-VEGF agents are effective in all lesion types, be it type 1, type 2, occult, or classic. However, if it's a type 3 CNV, the FA helps inform patients. In those situations, I will discuss with the patient that atrophy tends to be more common with that lesion type.

Dr. Williams: I also obtain FA on the initial visit as well as OCT-angiography (OCT-A). OCT-A allows us to evaluate choroidal neovascular membranes (CNVM) and distinguish between type 1 and type 2 CNVMs based on their presence below or above the retinal pigment epithelium (RPE).

Dr. Do: When we look at patients with abnormal lesions on OCT, one of the masquerading syndromes is a vitelliform

macular dystrophy that leads to a hyper-reflective subretinal deposit. In that setting, sometimes the FA in combination with fundus autofluorescence and OCT can help you make that diagnosis of the vitelliform lesion and spare the patient from multiple anti-VEGF injections.

Dr. Weng: That's a great point. I frequently receive referrals from nonretinal specialists with a pending diagnosis of neovascular AMD when, in fact, it's vitelliform and just needs to be monitored.

UNDERSTANDING AMD TREATMENT REGIMENS AND LIMITATIONS

Monthly treatment versus prn

Q | Dr. Weng: When you look across the major clinical trials with monthly dosing, patients experience VA gains between 7 and 11 letters during the course of a year. If everyone agrees that monthly treatment gives patients the best VA gains, why don't more of us do it?

Dr. Campochiaro: Because patients have difficulty adhering to monthly injections. If the patient is monocular and you effectively explain that aggressive treatment is their best chance of saving their vision, they will be motivated to come in for monthly injections. But a patient who has good vision in the other eye isn't as motivated, even if you explain they will have the best outcomes with monthly treatments. It's difficult for patients to come into the office every month. Treat-and-extend isn't as good, but it's good enough. That seems to be the default.

Dr. Weng: I agree; treat-and-extend is an attempt to have the best of both worlds. The prn approach hasn't given us as good visual acuity outcomes and monthly treatment has too high of a treatment burden.

Dr. Williams: Many factors go into deciding a treatment interval: patient age, number of comorbidities, transportation, their mobility, and out-of-pocket expenses, among others. Many patients fear injections, even if it's not particularly painful. The stress and anxiety that goes along with it cannot be understated. Even when patients understand how important it is to get the injections, it can be challenging for them to keep all those appointments. People also become ill and are hospitalized.

Dr. Do: There is one scenario in which we would aggressively treat with near monthly administration of a VEGF inhibitor. That is for a patient with significant, persistent intraretinal fluid that is affecting their visual acuity. We must remember that you should extend only if you feel the CNV is controlled and not active. If the CNV is still active and the patient isn't improving, we shouldn't extend.

Dr. Weng: That's an important point, Dr. Do. Although most patients are on a treat-and-extend regimen, a significant

proportion of them cannot extend beyond 4 weeks. Technically, we do not classify this as fixed monthly dosing, it's treat-and-extend, but they end up needing monthly injections anyway.

Dr. Do: You are correct, Dr. Weng. It is a notable proportion of patients; about 20% of my patients need aggressive monthly treatment with either ranibizumab or aflibercept. This is why we need to develop better therapies that have longer duration of effectiveness.

Dr. Weng: I agree; about 15% of my patients are unable to extend beyond monthly intervals. Some patients cannot extend beyond 4 weeks without their CNV becoming active. Let's shift gears and talk about a prn regimen, which is a less commonly used approach. As-needed treatment is a reactive response; you treat when you see activity. One thing I find interesting is that it's difficult to identify a consistent definition. "As-needed" seems to mean different things to different people. I was taught that prn means you have the patient come back monthly but only inject based on OCT findings. If there is persistent or worsening fluid, they are treated.

Q | What are the benefits to prn dosing?

Dr. Williams: Many patients don't need monthly injections to do well. The real challenge is not the injection itself but getting patients to the clinic on a monthly basis. The idea of reducing the injection burden is attractive to both retinal specialists and patients. To be most advantageous for patients, prn would require monthly appointments to assess the CNV. If the OCT looks good, you'd just skip the injection for those visits. The benefit of reducing the injections is countered by how frequently patients have to return to the clinic for an evaluation.

Dr. Weng: That's a great point. All of us share and appreciate the pure definition of prn but it's impractical to implement in a real-world setting because many do not bring patients in every month for that visit. Instead, patients are often followed more sporadically, which is why "real-world" prn doesn't lead to the most optimal visual acuity outcomes. However, if you look at studies such as PRONTO, you can achieve visual acuity outcomes with prn that are comparable to those seen in monthly injection trials.⁹ The injection burden is reduced, but not the appointment burden. As you all know, PRONTO had no comparator arm and patients were strictly followed monthly. Other studies that have looked at this include HARBOR, CATT, and IVAN.^{7,10,11} They may not have demonstrated statistically significant differences in visual acuity gain, but there were trends of higher gains with monthly injections.

Dr. Do: I rarely use prn. When I do, it's in patients who have CNV caused by other diseases such as high myopia. Those lesions are smaller, they tend to respond very well, and those eyes don't

require chronic treatment. As-needed treatment is not beneficial for most patients with neovascular AMD.

Dr. Campochiaro: The concept of prn came about because we initially didn't have a good understanding of neovascular AMD. We didn't know that the expression would be sustained for the remainder of most patient's lives, and we were concerned with overtreatment. A prn regimen offers a way to determine if expression has gone down and if an injection can be skipped. Some patients may not require injections for a period of time, but then they'll have a sudden recurrence. It's not predictable. Then if they don't come in immediately, they may have some permanent reduction in vision. This is an all-too-common scenario, which is why most retinal specialists have stopped using prn.

Treat-and-extend treatment paradigm

Dr. Weng: Several studies have looked at treat-and-extend. TREX-AMD, LUCAS, CANTREAT, ATLAS, and ALTAIR have shown that a treat-and-extend approach can lead to noninferior or comparable outcomes to monthly injections.¹²⁻¹⁶ I see treat-and-extend as the "Goldilocks" regimen; patients achieve good visual acuity outcomes without the heavy treatment burden of monthly injections and more reliable, consistent vision gains than a prn approach. With treat-and-extend, we generally start with a loading period of a certain number of injections and then extend by 2 weeks at a time. The interval is guided by OCT; if the patient is stable or has no fluid, you can extend.

Q | Does anyone deviate from this typical treat-and-extend regimen? For example, does everyone use loading doses? What is the maximum interval to which you feel comfortable extending?

Dr. Williams: I typically use three loading doses, but I will continue monthly treatment until the intraretinal fluid resolves. At that point, I'll extend for 2 weeks at a time, but sometimes I'll go slower if it took a long time for the fluid and exudation to resolve. I usually extend to 12 weeks, although there are some patients who can extend to 16 weeks if they've been stable at 12-week intervals for a year.

Dr. Campochiaro: My approach is very similar, with the one difference being that I consider visual acuity when determining the treatment interval. If the patient has very good visual acuity, I'm hesitant to go beyond 8 weeks. If a patient's VA is 20/80 to 20/100, I'm more inclined to extend to 12 weeks. I'm hesitant to stop treatment unless a patient's vision is such that I feel they're not gaining great benefit from injections.

Dr. Do: I agree with these treat-and-extend strategies. Only a minority of patients can be extended to quarterly injections.

Generally speaking, ranibizumab and bevacizumab do not have the durability to extend beyond 8 weeks. A minority of patients can extend to 16 weeks on aflibercept.

Dr. Weng: About 15 to 20% of my patients can extend to 12 weeks, which is similar to what was found in the TREX-AMD study.¹² By the 2-year time point, only 17% patients were able to achieve a quarterly dosing interval. If you look at some of the other treat-and-extend studies like LUCAS, TREND, and CANTREAT, less than half of patients were able to reach 12-week intervals.^{13,14,17} It's still a fleeting target for us to get patients to quarterly injections. Interestingly, if you look at TREX-AMD, patients in the treat-and-extend arm still had a mean of 10 injections over the course of the first year.¹² With the treat-and-extend approach, you're reducing the burden, but maybe not by as much as you may think.

Let's look at some of the real-world data we have from large database studies.¹⁸⁻²⁰ Patients in clinical trials receive 10 to 13 injections a year, but the truth of the matter is that real-world patients get half of that—five to seven injections a year, sometimes as few as two per year. As a result, most patients lose vision over a long period of time. That is a complicated observation that's probably due to many different factors. But it is, at least in part, due to undertreatment.

Q | Why are patients undertreated in the real world, with all of the effective therapies we have?

Dr. Campochiaro: We've talked about the burden of coming to the clinic, which is a key factor. Life gets in the way. Patients get sick, they break their leg, they have trouble with transportation. Patients really don't like injections. Even my compliant patients say they hate it. Very few patients are enthusiastic about injections.

Dr. Weng: What role do we, as providers, play in undertreatment?

Dr. Williams: I can't speak for every other retinal specialist, but sometimes patients' injection schedules can be altered by your schedule. You're out of the office, so the patient is extended an extra week. There's often an emotional component to injections for the patient. The physician extends a little bit, and then a little bit more because the patient really doesn't like injections. Or perhaps there's a negotiation to make sure you're getting your patients to come back, so you extend them a bit more than you should and accept the risk. No retinal specialist enjoys this, but sometimes you have to negotiate the time frame to convince patients return to the clinic at all.²¹

Dr. Weng: I also find that compliance tends to be very good initially, when patients are on that steep part of the curve where they're actually gaining visual acuity rapidly. However, once they've stabilized and we've moved to the maintenance phase, compliance wanes. No one wants to get a needle in their eye.



"Compliance is multifactorial and complicated. The burden is not only on the patient, but the patient's family because they rely on their caregivers for transportation."

—Diana Do, MD

Providers have become a bit numb to that because we give so many injections every day, but we aren't the ones on the receiving end. I try to imagine what it's like to come in every month for an injection, and I can definitely see why patients are fearful.

Dr. Do: Compliance is multifactorial and complicated.^{22,23} The burden is not only on the patient, but the patient's family because they rely on their caregivers for transportation. There's certainly an unmet need to find more durable drugs that can last longer and allow patients to be treated less frequently while still having control of their ocular disease.

Dr. Weng: That's a great point. Family members and/or caregivers must take off work to bring patients to their appointments. All of these factors contribute to missed appointments and intervals that are longer than ideal. Compliance is such a major factor in how the disease progresses long-term. I took a deep dive recently, looking at compliance in the setting of AMD. We oftentimes discuss compliance in the setting of our patients with diabetic retinopathy and diabetic macular edema considering those patients have unique struggles with socioeconomic, education level, and a general understanding of their disease.²⁴ But I was surprised to realize that compliance in the AMD population is not much better. One study from the Wills Eye group²⁵ found there was a loss to follow-up (LTFU) rate of 22.2% over 1 year among neovascular AMD patients who were receiving anti-VEGF injections. If you look at longer time horizons, those rates can exceed 50%. But being so busy, we may not even notice because you might not necessarily think of patients who don't show up to your clinic.

Q | Has anyone looked at the LTFU rate in this patient group in their own practice?

Dr. Campochiaro: I haven't, but I think these are excellent points. It's hard to keep track of patients. In my practice, we do

have a system in place in which a patient receives a call if they've missed an appointment and sometimes one call will get them into the office. But I don't have a good handle on how many patients are LTFU in my practice.

Dr. Williams: I've looked at LTFU in a roundabout way. I also do ocular oncology, and once the COVID-19 pandemic hit, we were moving patients around and paying close attention to our ocular tumor patients because we wanted to ensure we weren't missing them during this time. At the same time, we started looking at our patients who were receiving regular injections. We did a deep dive into the numbers and determined the LTFU rate during the pandemic was about 20%.

Dr. Weng: Unfortunately, sometimes it's out of sight, out of mind. We have to do more. A nontrivial percentage of my patients don't return, especially over longer periods of time. I think all of us can conclude, after this discussion, that longer durability agents can really help our current situation by alleviating some of the treatment burden, avoiding undertreatment, and thereby preventing some of the suboptimal visual acuity outcomes. What else is on your wish list?

Dr. Campochiaro: We always want more efficacy. Some patients still have fluid with monthly injections. Some of those patients don't do well. Other patients can maintain visual acuity pretty well for long periods of time despite subretinal fluid. But particularly patients who have sustained intraretinal fluid tend to lose vision over time. We're not at the ceiling yet for efficacy.

Dr. Do: On my wish list is an agent that blocks VEGF and can eliminate or prevent fibrosis and macular atrophy. Those two factors, the fibrosis and macular atrophy, can ultimately cause patients to lose vision in the long-term. We don't have good solutions for those.

THE WET AMD PIPELINE

Faricimab

Q | Dr. Weng: Faricimab is a bispecific molecule that targets both VEGF-A and Ang-2, which is involved in the Tie-2 pathway.²⁶⁻²⁸ What do we know about faricimab based on recent data?

Dr. Do: Faricimab is an exciting new drug in late-stage development. Faricimab is a novel bispecific antibody developed for the treatment of neovascular AMD. It blocks both VEGF-A and Ang-2. Faricimab is delivered as an intravitreal injection and be given in the clinic. The recent phase 3 clinical data was very positive. The two clinical trials in the phase 3 program are TENAYA (NCT03823287) and LUCERNE (NCT03823300).²⁹ These trials evaluated faricimab head-to-head against aflibercept. Eyes randomized to faricimab were first given four loading doses, and

then eyes were moved to fixed intervals of either every 2-, 3-, or 4-month dosing based on disease activity. The comparator arm was aflibercept given on-label, three loading doses, and then administered every 2 months. Both of these studies met the primary endpoint in that faricimab-treated eyes had visual acuity gains that were noninferior to those eyes treated with aflibercept.³⁰ More importantly, these studies also looked at the durability of faricimab. A total of 45% of patients treated in the TENAYA and LUCERNE studies were able to be treated every 4 months with faricimab during the first year of follow-up. This would be a big improvement because other clinical trials have not evaluated this type of dosing interval. In addition, about 34% of patients in these clinical trials were extended to more than 3 months with faricimab. Therefore, faricimab has shown to be an exciting, novel agent that has the potential of providing noninferior visual acuity gains compared to aflibercept at a 3- to 4-month dosing interval.

Dr. Weng: Every 16 weeks (q16) is a new bar for us that has not been formally studied with our existing agents. Approximately half of patients in TENAYA and LUCERNE were able to meet that q16-week interval. If that bears out in the real world, that would be really exciting and potentially provide a meaningful decrease in the treatment burden for our patients. Based on our current data, does faricimab seem safe and well-tolerated? There was a slightly higher percentage of patients in the faricimab arm who had intraocular inflammation compared to aflibercept, but there was no vasculitis or occlusive retinitis. Given this, how would you integrate faricimab into your treatment approach? Is this an agent you would use first-line on treatment-naïve patients?

Dr. Do: Faricimab has several positive attributes. Because these studies were quite large, the safety aspect seems favorable. I would be comfortable using this novel agent in both treatment-naïve wet AMD patients and also in previously treated patients who may have suboptimal response to other anti-VEGF agents.

Dr. Campochiaro: The data for faricimab are certainly interesting. In addition to the longer duration, there was OCT evidence showing greater drying and potentially greater efficacy in terms of reducing disease activity. These data are promising. However, we've learned through new agents that come to market that sometimes issues arise in the post-marketing period that weren't identified in clinical trials. Given this, I would not use faricimab in the first-line setting for treatment-naïve patients. I'd use it primarily for patients who are not getting an optimal response to other anti-VEGFs.

Dr. Weng: It's important to note that even our large phase 3 trials do not include hundreds of thousands of patients, which is really what you need to detect rare events. We've learned that lesson through some of our recent drugs.

Port-delivery system with ranibizumab

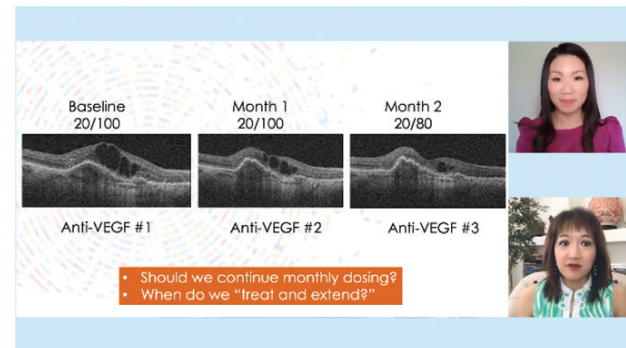
Q | Dr. Weng: Dr. Campochiaro, you've done a lot of work on the port delivery system (PDS) with ranibizumab. This potentially could be the first surgical device for neovascular AMD, which is exciting for all of us as surgeons.³¹ What do we know about the PDS based on recent data?

Dr. Campochiaro: The PDS is an implantable, refillable reservoir that continuously releases ranibizumab into the vitreous cavity. The surgery is straightforward, but there are details to keep in mind. First, the opening and closing of the conjunctiva should be done carefully to ensure good coverage of the septum. The scleral opening should be exactly 3.5 mm; larger incisions could lead to instability of the implant. If a larger opening occurs, and you should be detecting it by frequently measuring with a caliper during the procedure, then it's necessary to put a nylon suture to reduce the opening to 3.5 mm. The scleral incision is done carefully to expose the pars plana, which is then treated with laser photocoagulation to cauterize all vessels before incising it. Both the tenons capsule and the conjunctiva should be firmly anchored at the limbus with two sutures, with good episcleral bites at the superior and inferior border of the edge so that it overlaps the peripheral cornea and is very tight against it. Complications can be minimized by adhering to these guidelines.

The LADDER trial compared the PDS filled with 10, 40, or 100 mg/mL of ranibizumab with monthly ranibizumab injections.^{32, 33} Patients received at least two injections of ranibizumab prior to baseline. The primary outcome was time to first refill exchange. The median time was 15.0, 13.0, and 8.7 months in 100, 40, and 10 mg/mL PDS groups. In the 100 mg/mL group, 80% of the patients did not require a refill exchange for 6 months or longer. The 100 mg/mL group also had comparable visual and anatomic outcomes as the monthly injection group at 9 months.

These data informed the design for the phase 3 ARCHWAY trial, which compared the PDS filled with 100 mg/mL ranibizumab with refill exchanges every 24 weeks with monthly injections of 0.5 mL ranibizumab in patients with neovascular AMD who were responsive to anti-VEGF treatment (NCT03677934).^{34,35} The baseline best-corrected visual acuity (BCVA) was 20/32 in each arm because they had received a mean of five anti-VEGF injections prior to baseline. The primary endpoint was the change in BCVA score from baseline averaged over weeks 36 and 40. ARCHWAY met its primary endpoint. Compared with the gain of 0.5 letters in the monthly injection arm, a gain of 0.2 letters in the PDS arm was noninferior and equivalent. The excellent baseline BCVA from prior treatment was well-maintained in each arm. A total of 98% of PDS patients did not receive a supplemental injection prior to the first refill exchange. The most frequent adverse event was conjunctival bleb, which occurred in 6.5% of patients. This isn't the type of conjunctival bleb that

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we're used to thinking of as a filtering bleb. In most instances, it was a thickening beneath the conjunctiva, and all were classified as not serious. Vitreous hemorrhage rate was 5.2%, and all resolved spontaneously without vitrectomy. Conjunctival retraction or erosion occurred in 11 patients, which was a significant problem. However, nine of 11 cases were addressed by conjunctival flap revision, alone or in combination with covering the implant flange with partial thickness cornea. There were four cases of endophthalmitis, three of which were related to conjunctival retraction. One patient had irreversible vision loss. The other three, though, did return to baseline, and two continued with refill exchanges. There was one device dislocation into the vitreous cavity during a refill exchange. When the PDS was removed, the BCVA returned to baseline. So, efficacy was really excellent, the complication rate was low, and ways to reduce complications were identified. The PDS will likely be approved by the FDA by the end of 2021 or the beginning of 2022.

Dr. Weng: It's exciting to think about a device like this that can really take us leaps and bounds further in durability. We're talking 6 months or longer for the vast majority of patients. Almost 99% of patients in ARCHWAY were able to reach the 6-month time-point before a mandated refill-exchange was given. The median time to refill was more than 15 months in LADDER. These are exciting and interesting data, and I think patients would appreciate that decrease in treatment and visit burden. Along those lines, if you implanted a patient with the PDS in the real world, how would you follow them? Would you feel comfortable going 6 months without bringing them in for an OCT or an exam?

Dr. Campochiaro: I will see patients 1 month after PDS implantation to make sure there's good conjunctival coverage and it's sealed well. Then I will see them 4 months after the implant to make sure they're still dry or that they have minimal fluid. I will then do the refill exchange at 6 months. If the patient goes the full 6 months without needing a refill exchange and shows very little fluid, I

will have them return in 5 months for a check and do the refill/exchange a month later for the next exchange. If a patient goes through two refill/exchanges with no macular fluid, I will start seeing them at 6-month intervals for refill/exchanges. Patients do need to be mindful of red eyes and pain; if either occurs, I need to see them immediately. The major value of a sustained-delivery technology is predictability. We have to be confident that durability will be similar in all patients. The PDS fits that bill.

Dr. Weng: The PDS requires surgery, which could pose a barrier for some patients. What factors would you consider in selecting ideal PDS patients?

Dr. Williams: There are a few factors I would consider. First, because we're concerned about the conjunctiva, I would be paying attention to a history of glaucoma, which could potentially cause an issue for surgery down the road. In myopic patients, I'd be thinking about a buckle in the future. Ideal patients for the PDS include patients who do well with injections but really don't like having injections and are motivated to proceed with surgery. I'd consider the PDS in patients who are older with no significant risk of long-term infection or conjunctival reaction.

Dr. Do: One potential downside to the PDS is that it requires a surgical implantation. My first-line treatment is still an office-based intravitreal injection in patients with new onset wet AMD. I want to aggressively treat them that day to prevent further vision loss. Because of this, office based intravitreal anti-VEGF medicines will still be the mainstay for the vast majority of retinal specialists. The PDS will be a second- or third-line agent in my hands.

OPT-302

Q | Dr. Weng: Let's move on to OPT-302, which is an interesting molecule that blocks VEGF-C and VEGF-D. Dr. Do, what can you tell us about OPT-302?

Dr. Do: OPT-302 is a unique molecule because unlike our current VEGF inhibitors that block VEGF-A, this trap molecule blocks VEGF-C and VEGF-D.²⁸ The idea is that combination therapy of OPT-302 and another VEGF-A inhibitor may have the potential of more complete blockade of the angiogenic pathway and help those patients who have suboptimal responses to our current VEGF inhibitors. Earlier phase 2 data were very promising and, surprisingly, showed a statistically significant superior mean gain in visual acuity in patients who were given the combination of OPT-302 with ranibizumab compared to ranibizumab monotherapy.³⁶ Phase 3 clinical trials are now underway (NCT04757610 and NCT04757636). They are looking for superiority in visual acuity with OPT-302 given in combination with either aflibercept or ranibizumab compared, head-to-head, with aflibercept or ranibizumab monotherapy. I think this is an exciting new pathway that we're evaluating. It will be interesting to see if this drug can help make superior visual acuity gains.



"I'd consider the PDS in patients who are older with no significant risk of long-term infection or conjunctival reaction."

—Basil K. Williams Jr, MD

Dr. Weng: Do you think providers and patients would be willing to give and receive two injections instead of one? Are there any concerns that you're putting in a larger volume into the eye?

Dr. Do: Combination therapy has some disadvantages. Two separate injections could theoretically increase the risk for endophthalmitis. In addition, it is a slightly higher volume. So far there have been no serious adverse events related to the two-injection mechanism with the higher volume in the phase 2 trials. The phase 3 study will include more 900 patients, so we'll be able to get a better sense of the safety involved.

KSI-301

Q | Dr. Weng: Dr. Williams, what can you tell us about KSI-301?

Dr. Williams: KSI-301 uses a unique antibody biopolymer conjugant platform that is precision engineered for durability and efficacy. It takes the antibody, which has a specific, single site for anti-VEGF-A, and provides a stable link with the biopolymer, which has a molecular weight and is optically clear.²⁸ That combination gives you a set of integrated properties, which allows for a higher molar concentration of medication and a fast, systemic circulation clearance. DAZZLE is a phase 2b global, multicenter, randomized study of treatment-naïve wet AMD patients receiving either KSI-301, 5 mg, or 2 mg of aflibercept every 8 weeks (q8) (NCT04049266).³⁷ Both groups received three monthly loading doses. Patients in the aflibercept arm will continue with q8 dosing through 1 year. The KSI-301 group will be dosed at 12, 16, or 20 weeks, depending on the specific criteria of the study. The primary endpoint at 1 year is BCVA. Patients will be followed for 2 years. I'm very interested in seeing these data, as 66% of patients in the phase 1b trial were able to have a 6-month treatment-free interval at 1 year with a mean of 5 injections, including three loading doses. About 54% of patients required only one additional treatment after the

monthly loading dose. From that early phase 1b data, KSI-301 looks promising.³⁷ We'll be looking forward to DAZZLE results to see what happens there.

Dr. Weng: Given the safety profile we've seen so far, would you feel comfortable using KSI-301 in treatment-naïve patients if they can achieve such great durability?

Dr. Williams: The clinical trials haven't gotten to the point where I can speak with certainty, but there were only two cases of intraocular inflammation in the phase 1b trial. It was mild vitreous cell and there were no ischemic events. The patients who had intraocular inflammation responded to topical treatment. It's very early, and I'd be a hesitant to use this in the first-line setting initially. I'd want to wait to see what the results were in the real world over time.

GB-102

Q | Dr. Weng: And how about GB-102? There was topline data just released.

Dr. Williams: GB-102 is a small-molecule receptor.^{28,38} It's a sunitinib malate and tyrosine kinase inhibitor that provides pan-VEGF and placental growth factor inhibition. It's a proprietary microparticle formulation that gradually releases sunitinib and is designed to achieve a sustained therapeutic drug level. This medication is being studied in the phase 2b ALTISSIMO trial in patients who have had a previous diagnosis of wet AMD within 18 months of the study and who have received at least three injections of an anti-VEGF and have shown a response to that medication (NCT03953079).³⁹ The phase 2 trial was broken down in a 3:3:2 ratio. The phase 1 study looked at 32 patients with multiple doses: 0.25 mg, 0.5 mg, 1 mg, and 2 mg and determined that the 1-mg dose was the best approach.⁴⁰ However, in this study, about 30% had dispersion of the medication into the anterior chamber. As a result, the manufacturing process was optimized between the phase 1 and phase 2b studies.

For the phase 2b ALTISSIMO trial, researchers started with a 3:3:2 ratio, with group 1 receiving a 1-mg dose of GB-102 at baseline and at month 6; sham injections were given at months 2, 4, 8, and 10. Group 2 received a 2-mg dose of GB-102 at baseline. However, this group did not receive the planned 2-mg dose at 6 months because information from the phase 2a trial for macular edema showed a high rate of medication migration to the anterior chamber for the 2-mg dose. Enrollment in the phase 2b ALTISSIMO trial was temporarily paused. After a safety analysis of the phase 2a macular edema study, a decision was made to discontinue use of the 2-mg dose. As a result, all patients in group 2 received a 1-mg dose of GB-102 and sham injections at months 2, 4, 8, and 10. Group 3 received 2 mg of aflibercept at baseline and month 2, 4, 6, 8, and 10.

The primary endpoint was median time to first supportive

therapy. Preliminary topline data were released by Graybug recently and found that 48% of patients did not require supportive therapy for at least 6 months.⁴¹ A total of 62% of patients did not need supportive therapy for at least 4 months or more. Looking at secondary endpoints, the central subfield thickness was similar to the aflibercept group, and the BCVA was not powered to assess inferiority, but it did not seem to be as good as the aflibercept group. A little less than 10% of patients had anterior chamber dispersion of medications, and no adverse event required surgical intervention. At this point, 28 patients reached the endpoint successfully and will be followed for another 6 months.

Gene therapy

Q | Dr. Weng: Dr. Campochiaro, you've been very involved in gene therapy development at the basic science and clinical levels. Can you give us an overview of where we stand at this time?

Dr. Campochiaro: Gene therapy uses a vector to carry a gene into the nucleus of cells, so the cells produce a therapeutic protein. The most commonly used vector for ocular gene therapy is adeno-associated viral vectors (AAV). There are several serotypes that differ with regard to what they bind to on cell surfaces to enter cells. The more a particular cell expresses that receptor, the greater the cell entry and the expression of the therapeutic protein. AAV2 enters RPE cells and photoreceptors quite well. Voretigene neparvovec, which is approved for Leber congenital amaurosis, is an AAV2 vector. AAV8 is even more efficient than AAV2.⁴²

The best way to get a high-concentration of vector to contact the RPE and photoreceptors is by subretinal injection. This requires a vitrectomy and blowing a small hole in the retina to create a bleb, which is a focal detachment where RPE and photoreceptors are separated by fluid containing the vector. The fluid is rapidly absorbed, concentrating the vector, resulting in high-level infection or transduction; these terms are interchangeable. Photoreceptors and RPE in the region of the bleb express the transgene, but there's little or no expression outside the bleb. Suprachoroidal injection is a new route of delivery that also allows access to the RPE and photoreceptors without going to the operating room and detaching the retina.⁴³

After intravitreal injection, most AAV vectors bind to the internal limiting membrane, which limits expression and penetration into the retina. But the Schaffer Research Group at the University of California, Berkeley, has used directed evolution to develop AAV vectors with reduced binding to the internal limiting membrane,⁴⁴ which results in greater penetration into the retina, and much higher expression after intravitreal injection. One of those vectors is called AAV7m8.⁴⁵

RGX-314 is an AAV8 vector that expresses an anti-VEGF Fab fragment similar to ranibizumab.^{28,46} The manufacturer sponsored a trial testing subretinal injection of RGX-314 in pseudophakic patients with neovascular AMD who received four or

more anti-VEGF injections in the 8 months prior to enrollment.²⁸ Subretinal injection of RGX-314 was well-tolerated with no drug-related severe adverse events. There was minimal inflammation. Subretinal injection of 6×10^{10} genome copies (GC)/eye or higher resulted in stable or improved BCVA a year after injection. Cohort 3 received 6×10^{10} GC/eye, cohort 4 received 1.6×10^{11} GC/eye, and cohort 5 received 2.5×10^{11} GC/eye. Three of six patients in cohort 3, three of 12 in cohort 4, and eight of 12 in cohort 5 did not receive rescue injections. Mean RGX-314 protein level in the aqueous in cohort 3 was 200 ng/mL at 6 and 12 months. In cohorts 4 and 5, it was 655 ng/mL and 848 ng/mL at 6 months and 420 ng/mL and 457 ng/mL at 1 year, respectively. Data are now available through 2 years for cohort 3 and there was continued improvement in BCVA with stable production of the RGX-314 protein. Four of six patients did not require rescue injections after the 9-month timepoint.²⁸

The first of two planned phase 2b/3 trials, ATMOSPHERE (NCT04704921), has started. The goal is to enroll 700 patients with neovascular AMD. In one trial, patients will be enrolled across two RGX-314 dose arms versus ranibizumab, with the primary endpoint of noninferiority to ranibizumab based on BCVA at 1 year. The second trial is the same design but RGX-314 will be compared against aflibercept. The phase 2 AAVIATE trial (NCT0454653) is currently enrolling patients with neovascular AMD and will compare the suprachoroidal injection of RGX-314 to monthly injections of ranibizumab at 40 weeks.²⁸ The phase 2 ALTITUDE trial is enrolling patients with diabetic retinopathy and is designed to determine the proportion of patients with a 2-step improvement in DRSS 48 weeks after suprachoroidal injection (NCT04567550).

ADVM-022 is an AAV7m8 vector that expresses aflibercept. The manufacturer is sponsoring the OPTIC trial testing ADVM-022 in patients with neovascular AMD (NCT03748784).²⁸ There were four cohorts with six patients in cohorts 1 and 2 and nine patients in Cohorts 3 and 4. Cohorts 1 and 4 received intravitreal injection of 6×10^{11} GC/eye. Cohorts 2 and 3 received 2×10^{11} GC/eye. Cohorts 1 and 2 were given a 13-day course of oral steroid, and cohorts 3 and 4 were given topical steroids. Patients required many anti-VEGF injections prior to enrollment and very few injections after the intravitreal injection of ADVM-022. There were two serious adverse events, recurrent moderate uveitis and retinal detachment. Researchers determined that the uveitis was caused by ADVM-022 but the retinal detachment was not. In cohort 1, BCVA was stable through 72 weeks with no rescue injections, but inflammation was present at 20 weeks in five of six patients in cohorts 1 and 2 and 5 in six of nine patients in cohort 3. Some patients developed inflammation after 30 weeks, which is concerning because it's hard to invoke the vector as the source and it could be an immune reaction to transduced cells.²⁸ ADVM-022 was being tested in patients with DME in the INFINITY trial (NCT04418427). The trial was halted when, 3 weeks after intravitreal injection of 6×10^{11} GC/eye, a patient developed pan uveitis and hypotony with loss of vision.⁴⁷ At this point, there are some

intriguing efficacy signals, but the safety of intravitreal injection of ADVM-022 is uncertain.

HMR59 is an AVV2 vector that expresses a soluble form of CD59, which blocks the formation of membrane attack complex. It's being tested by intravitreal injection in two trials; one in patients with advanced dry AMD and geographic atrophy (HMR-1001; NCT03144999) and one in patients with new-onset wet AMD (HMR-1002; NCT03585556).

To summarize, there are several trials investigating gene therapy, but it's still early. We don't have a handle on the data. We have intriguing early findings, but we need more data.

Dr. Weng: I agree. We were surprised to see what was observed with ADVM-022 in the INFINITY trial. But it reminds us this is new territory for us as a scientific community. We are learning as we go, and safety must always be of utmost priority. Based on what we've seen so far, the subretinal route seems to be pretty well-tolerated with not as much inflammation, whereas intravitreal injections tend to mount a more robust, immunogenic and inflammatory response. Dr. Campochiaro, what is the inflammation and immunogenic response like with the suprachoroidal route as compared with the subretinal and intravitreal routes?

Dr. Campochiaro: Data on the suprachoroidal route are still early, but in a primate study there was very little inflammation with suprachoroidal injection of RGX-314.⁴³ From a theoretical standpoint, you're right; there is more exposure to the immune system. We don't completely understand the situation with intravitreal injections. It seems dose related, but when you go up to a certain amount of vector, there can be a pretty substantial inflammatory response. We're going to be watching suprachoroidal injections closely to see if there's anything similar. But in the preclinical studies, it appeared there was less inflammation than what has generally been seen in preclinical studies with intravitreal injection.

CASE 1: VISUAL ACUITY GAINS WITH MONTHLY RANIBIZUMAB INJECTIONS

Dr. Weng: Our first case is a great example of the effectiveness of strict monthly treatment with ranibizumab for retinal vein occlusion (RVO) and neovascular AMD.

Dr. Campochiaro: This patient presented with central RVO in 2006 and was entered in our very first trial testing ranibizumab in patients with RVO. Because we did not fully understand the disease process at the time, patients received three injections one month apart. Then we pivoted to prn without monthly visits to reduce the injection burden. His peak VA was 20/32. The first line of Figure 1 shows the first 4 years of treatment. The patient had a lot of recurrent edema, but his VA was still 20/30 to 20/40 at the end of the 4-year period. The patient then entered other clinical trials during the next 4 years, including one in which he

received panretinal photocoagulation (PRP) to reduce the need for injections. However, scatter photocoagulation was not effective in reducing injection need. The patient was still treated prn without monthly visits, and his vision was about 20/40 at the end of the 6 years. During the next 4 years, his vision began to drop. He developed neovascular AMD in his fellow eye. I was very aggressive with treatment because he already had compromised vision in the other eye. We did monthly injections for both eyes, and the edema in the right eye was well-controlled during that period; his VA was 20/63. If you don't treat aggressively, you gradually lose vision over time. Figure 2 shows the fellow eye. He started with

20/20 vision and is still 20/20 after 3 years of monthly injections. He is a highly motivated patient, but still occasionally misses visits. But fortunately, with close to monthly injections, he's maintained really good VA.

Dr. Weng: This case wonderfully illustrates the effectiveness of strict monthly therapy in patients who already have a compromised eye. This patient had a great result, but unfortunately that's not the case for everyone, and many patients have eventual waning of visual acuity. Dr. Campochiaro, would you consider one of our new therapies in the pipeline for a patient who is doing



Figure 1. Case 1: BCVA and central subfield thickness (CST) in a patient with central retinal vein occlusion (right eye) followed over 11.5 years.



Figure 2. Case 1: BCVA and CST in fellow eye wet AMD.

this well on monthly injections? Or would you be hesitant to try something new given the contralateral compromised eye?

Dr. Campochiaro: For this patient, I'd hold off longer than in other patients on using something new. These diseases need to be treated with sustained suppression of VEGF. I fully expect that approach will result in better outcomes in the long-term. But this patient is really good about coming in, and we're having success under the current paradigm. He wouldn't be the first patient I try a new therapy on, but at some point, I'd offer it.

CASE 2: MONTHLY TREATMENT, PERSISTENT FLUID

Dr. Do: This is a 73-year-old man with a history of macular degeneration. He came in with decreased vision in his right eye for 1 week. His VA in that eye was 20/100. The fundus photograph shows drusen, elevation of the RPE, and edema through the macula (Figure 3). The corresponding OCT confirms these findings. There's significant intraretinal fluid and a pigment epithelial detachment (PED) involving the foveal center. Can we predict the patient's prognosis based on the OCT or how they present? What dosing strategy would you recommend for this patient?

Dr. Weng: There is clearly intraretinal fluid here. We are learning more and more about different types of fluid, and that we may be able to tolerate some types of fluid more than others.⁴⁸ Does the fluid type change how aggressive you are in treating this particular patient?

Dr. Campochiaro: Intraretinal fluid is more damaging than subretinal fluid, therefore you need to do everything you can to reduce and minimize intraretinal fluid. I'd be aggressive with this patient, starting with monthly injections. I also consider starting him with aflibercept rather than bevacizumab.

Dr. Do: Figure 4 shows a comparison of the baseline OCT to months 1 and 2 of therapy. After the first injection, VA remains 20/100. There is a reduction in intraretinal cystic fluid, but the PED is still present. At month 2, the patient's VA improves to 20/80. There is continued resorption of the intraretinal fluid, although some of the intraretinal fluid remains. The PED is, again, still present. He has a third monthly injection. Would anyone feel comfortable extending the interval, or should we continue with monthly treatment?

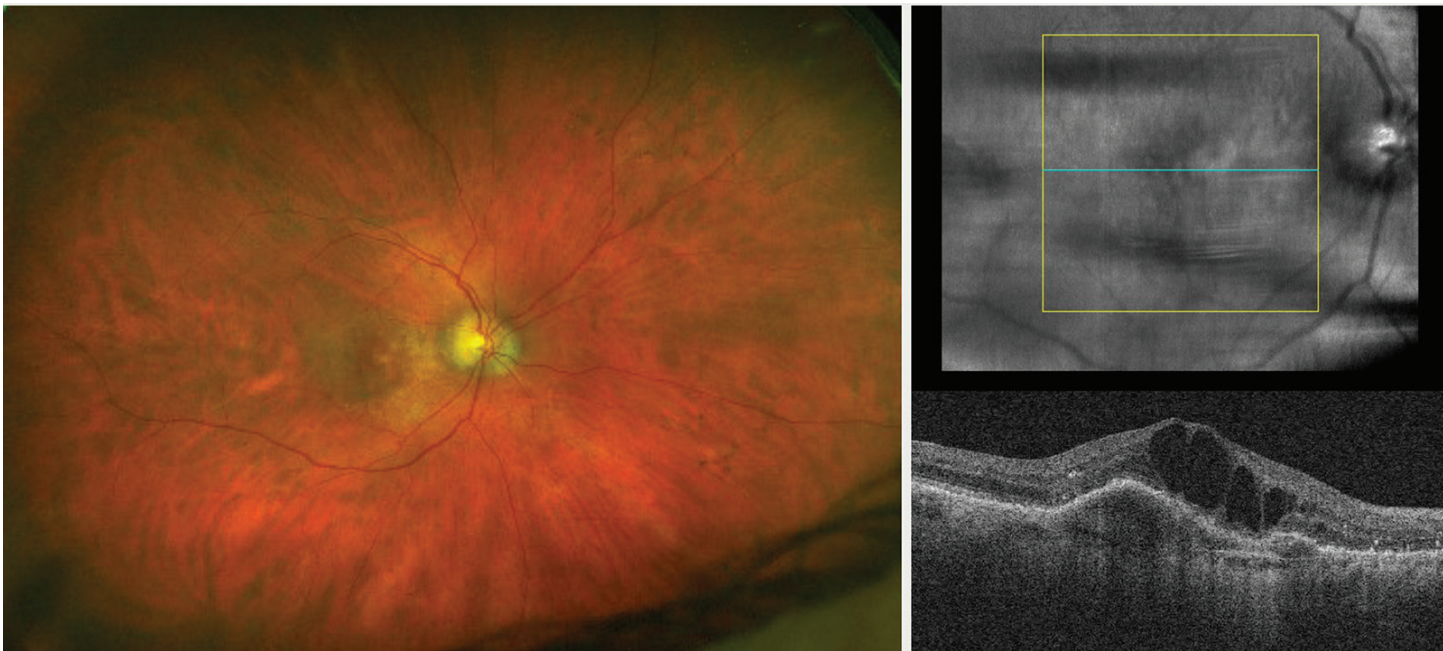


Figure 3. Case 2: Baseline fundus and OCT (right eye).

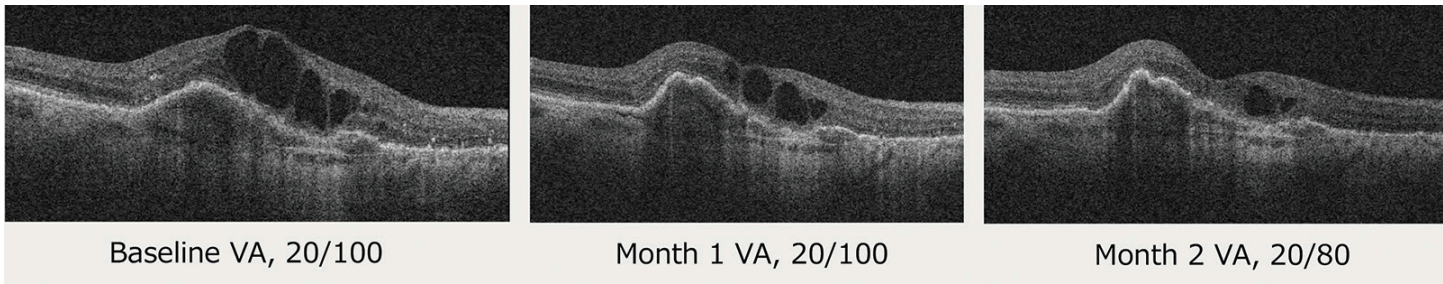


Figure 4. Case 2: Comparison of baseline OCT to months 1 and months 2 of therapy.

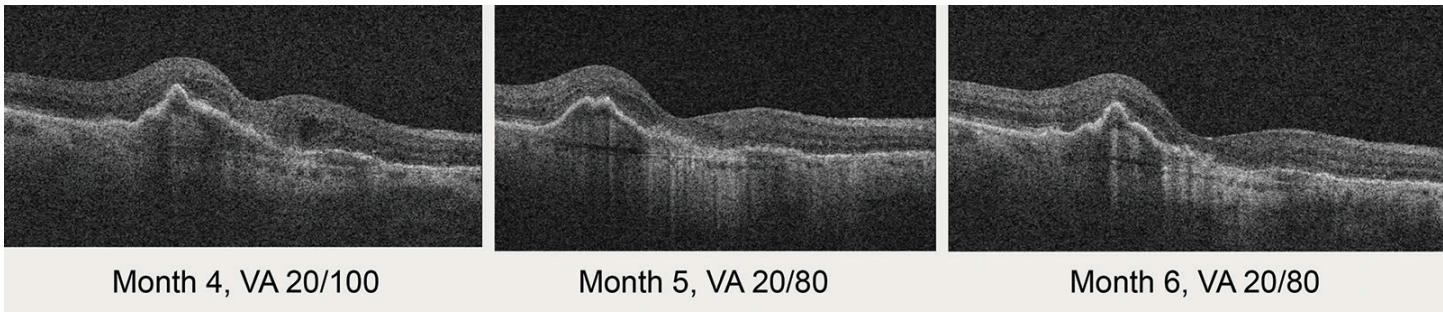


Figure 5. Case 2: OCT month 4 to month 6 of treatment.

Dr. Weng: I would continue with monthly treatment because we know that intraretinal fluid is damaging. I tend to want to see complete resolution of intraretinal fluid, but am less stringent when it comes to subretinal fluid, especially in the setting of stable fluid and vision. But I would continue to advocate for monthly therapy in this patient who has persistent intraretinal fluid, even if he's improving.

Dr. Do: We continued monthly therapy. After the fourth injection, his VA remained 20/80 and there is almost near resolution of intraretinal fluid (Figure 5). I continue with monthly anti-VEGF therapy because there is still a PED. At month 6, VA remains 20/80. There's even less intraretinal fluid. Now, at this stage, who would extend the interval?

Dr. Campochiaro: I would consider extending the interval at this point. I don't treat based on PEDs, and the retina is pretty dry.

Dr. Do: If we had any of the newer agents in the pipeline available, such as faricimab or the PDS, would you use any of those agents in this patient?

Dr. Williams: I'm not sure I would recommend anything like that at this point. I would start to extend and see what happened. However, if we extended and the fluid came back, I may consider a new agent.

Dr. Do: I am still aggressively treating this patient to try to improve this vision, which is hovering around 20/70, 20/80. The OCT shows some disruption of the outer retina under the fovea, which limits how much vision will improve.

CASE 3: TREATING A MONOCULAR PATIENT WITH WET AMD WHO IS LTFU

Dr. Williams: This is an 85-year-old woman who developed wet AMD in her right eye while living out of state after her husband died (Figure 6). She received frequent intravitreal injections of various types during that time frame. However, every time she was extended to 8 weeks or more, the fluid increased. The fluid would gradually resolve, but her vision would decrease with each recurrence. She moved to town a week before I saw her. She presented with a change in vision in her left eye, which was previously unaffected (Figure 7). Her VA was 20/50, down from 20/25 while being seen by another specialist. We started her with monthly bevacizumab injections and she did fairly well. Her VA fluctuated between 20/50 and 20/70 depending on the visit. She was injected every 4 to 6 weeks for the first 16 or 17 months. Unfortunately, she was lost to follow-up for 5 months because she contracted COVID-19 and was hospitalized. When she returned, her VA decreased to 20/80 (Figure 8). She's very upset and

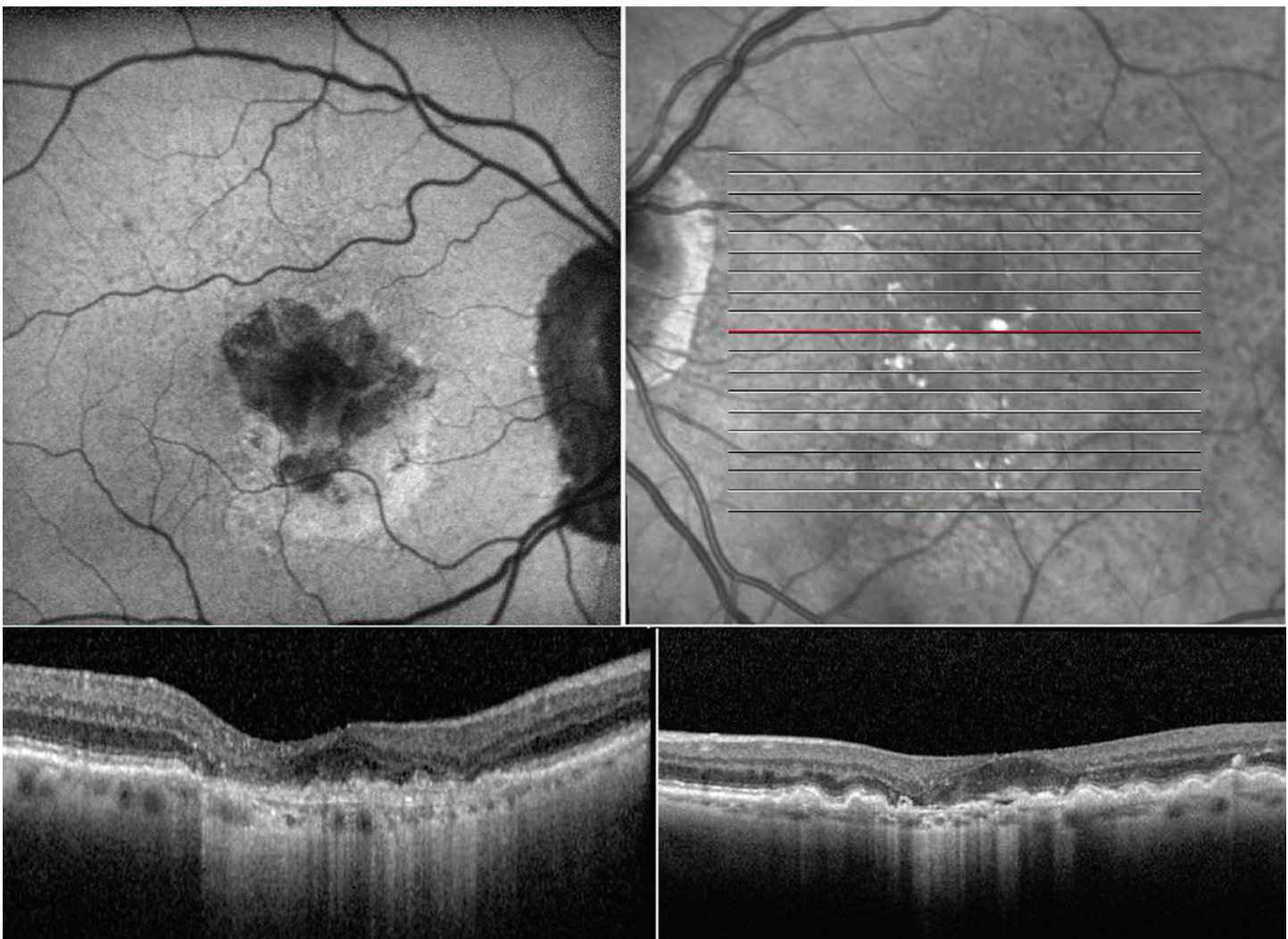


Figure 6. Case 3: Baseline imaging at the patient's first visit with Dr. Williams (right and left eyes, respectively).

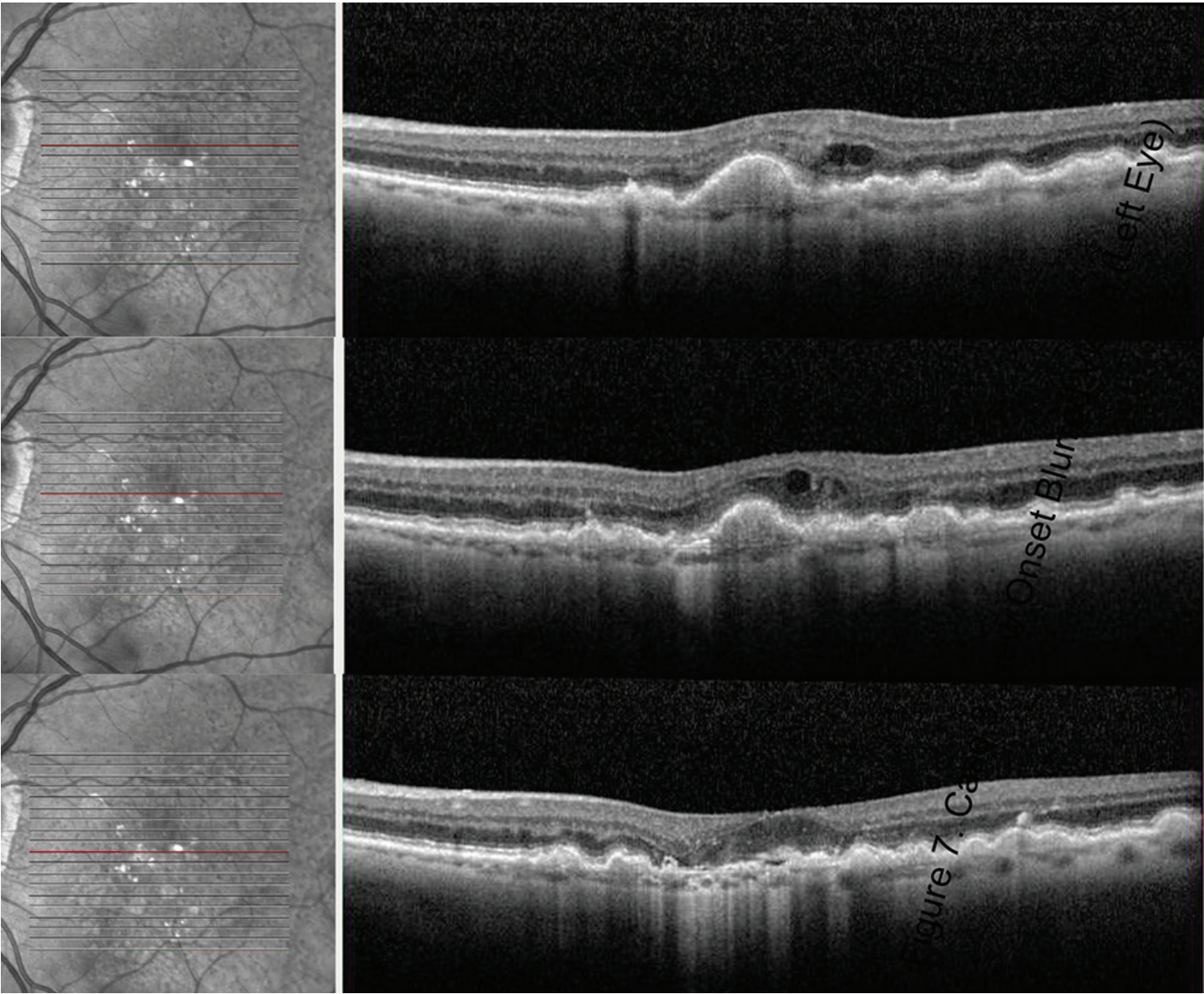


Figure 7. Case 3: New-onset blurred vision (left eye).

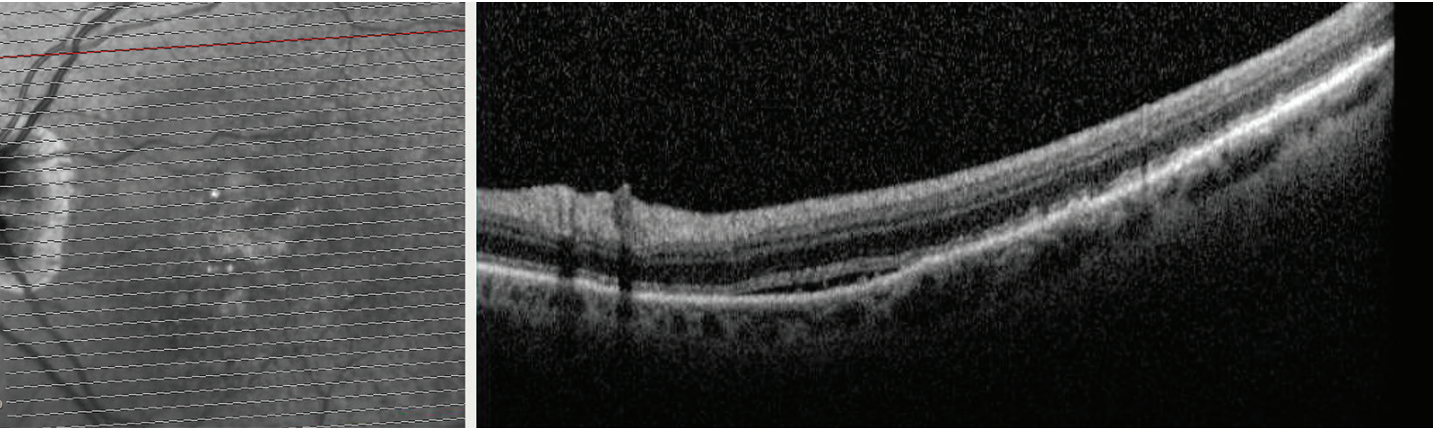


Figure 8. Case 3: Imaging of the left eye after 5 months lost to follow-up.

concerned her vision will not improve. We switched her to aflibercept and continued with monthly injections. Her VA gradually improved to 20/50. She then missed her next monthly injection because she had no transportation, causing the fluid to recur. Her VA is now 20/150 and we are planning to treat her again in a few of weeks.

This case illustrates how challenging it can be to treat a monocular patient with our current options, given the variety of reasons why appointments can be missed. We need agents with longer durability in the event a patient is lost to follow-up.

Dr. Weng: This is a great example of someone who could benefit dramatically from one of agents with longer durability. Would you try an agent in the pipeline on this patient?

Dr. Williams: Yes, I'd have the conversation with this patient. I think she'd be highly motivated to try something different.

Dr. Weng: When patients are LTFU for months and return with recurrent fluid, do you start over with loading doses?

Dr. Do: I would be very cautious and follow this patient monthly until the disease activity was under control, especially because this is her only seeing eye. I would extend very cautiously once there was no intraretinal fluid or activity.

Dr. Weng: I'd like to thank our panel for their wonderful insights and comments and for providing such excellent information on pipeline agents for retinal diseases. ■

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INSTRUCTIONS FOR CME CREDIT

To receive credit, you must complete the attached 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. To answer these questions online and receive real-time results, please go to <https://evolvemeded.com/course/2127-1supp>. If you experience problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically, therefore, please provide your email address below.

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

Full Name _____

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Address/P.O. Box _____

City _____ State/Country _____ Zip/Postal Code _____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

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

LEARNING OBJECTIVES

Did the program meet the following educational objectives?

Describe the pros and cons of current therapy options for wet age-related macular degeneration.

Articulate the challenges facing retina specialists related to the complexities of managing patients with wet age-related macular degeneration.

Assess pipeline candidates under investigation for this patient population.

Agree

Neutral

Disagree

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to assess pipeline candidates under investigation for patients with diabetic retinopathy (DR, diabetic macular edema (DME, and wet age-related macular degeneration (AMD) (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
2. A 66-year-old man with wet AMD and 20/40 vision cannot extend beyond 8 weeks with ranibizumab. He has been adherent to therapy but is starting to complain about the injection burden. What novel therapy may be appropriate (if approved)?
 - a. Faricimab
 - b. Gene therapy
 - c. Port delivery system (PDS) with ranibizumab
 - d. All of the above
3. According to pivotal clinical trials, what treatment schedule will achieve the best gains in visual acuity for patients with wet AMD?
 - a. Monthly
 - b. Treat-and-extend
 - c. As-needed (prn)
 - d. There is no difference in visual acuity gains between treatment schedules
4. Which is TRUE regarding studies comparing treat-and-extend versus other regimens?
 - a. Treat-and-extend regimens lead to significantly inferior visual outcomes compared to monthly.
 - b. In most studies, treat-and-extend reduces the visit/injection burden by approximately 50% compared to monthly.
 - c. Treat-and-extend regimens reduce the visit/injection burden without significantly compromising visual acuity outcomes in comparison to prn or monthly regimens.
 - d. Treat-and-extend regimens lead to inferior visual outcomes compared to prn regimens.
5. Approximately _____ of patients with wet AMD who are receiving anti-VEGF injections are lost to follow-up in the first year of treatment.
 - a. 14%
 - b. 22%
 - c. 36%
 - d. 52%
6. A 72-year-old White female with coronary artery disease, glaucoma, and obesity continues to have persistent subretinal fluid with monthly injections of aflibercept. She previously had suboptimal responses with bevacizumab and ranibizumab. The fluid has improved with aflibercept but has not resolved. She relies on her daughter for transportation to and from appointments, and the treatment burden on the family is substantial. Assuming that faricimab is FDA-approved, which statement might you use to counsel her in potentially switching agents?
 - a. Faricimab is injected into the suprachoroidal space and offers a durability of 6 months.
 - b. In the phase 3 TENAYA and LUCERNE studies, nearly 80% of wet AMD patients were able to achieve a q16-week interval.
 - c. Faricimab is a bispecific molecule that targets VEGF-A, but also targets Ang-2 which may help increase vascular stability.
 - d. Faricimab could potentially offer better efficacy and durability, but patients had significantly higher rates of retinal vasculitis in the phase 2 and phase 3 studies.
7. Which of the descriptions represents the most ideal patient for the PDS with ranibizumab?
 - a. A treatment-naïve patient with many systemic comorbidities and a history of glaucoma.
 - b. A patient who is doing well on anti-VEGF treatment but fearful of injections and has expressed interest in fewer visits and/or injections.
 - c. A patient who is doing well on quarterly injections of anti-VEGF with no significant socioeconomic challenges.
 - d. A patient who has demonstrated a suboptimal response to ranibizumab in the past, but whose disease activity is well controlled on aflibercept every 10 weeks.
8. ADVIM-022 and RGX-314 are gene therapies that use _____ to carry a gene into the nucleus of cells.
 - a. A viral vector
 - b. A nonviral vector
 - c. DNA
 - d. Cell therapy
9. In the LADDER phase 2 study of PDS, the median time to refill in the highest-dose arm was _____.
 - a. 6 months
 - b. 9 months
 - c. 12 months
 - d. 15 months
10. Which statement best describes OPT-302?
 - a. OPT-302 is a coformulation drug that blocks VEGF-A and VEGF-C/D.
 - b. OPT-302 is a tyrosine kinase inhibitor that provides pan-VEGF blockade.
 - c. In a phase 2b study, OPT-302 used in combination with ranibizumab lead to superior visual acuity outcomes at 24 weeks in wet AMD patients compared to ranibizumab monotherapy.
 - d. OPT-302 is now being studied in two phase 3 studies that will compare visual outcomes of OPT-302 used in combination with ranibizumab/aflibercept versus OPT-302 monotherapy.

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

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

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

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

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

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

Change in pharmaceutical therapy ____ Change in nonpharmaceutical therapy ____

Change in diagnostic testing ____ Choice of treatment/management approach ____

Change in current practice for referral ____ Change in differential diagnosis ____

My practice has been reinforced ____ I do not plan to implement any new changes in practice ____

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

____ Cost	____ Lack of opportunity (patients)	____ No barriers
____ Lack of consensus or professional guidelines	____ Reimbursement/insurance issues	Other. Please specify: _____
____ Lack of administrative support	____ Lack of resources (equipment)	_____
____ Lack of experience		_____
____ Lack of time to assess/counsel patients	____ Patient compliance issues	

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

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

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

Additional comments:

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

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

