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ACHIEVING NEW HEIGHTS OF DURABILITY IN RETINA

What's in Store for Retina Treatments and the Patients Who Need Them

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Content Source

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

Activity Description

This supplement summarizes a roundtable discussion among retina experts as they review how current therapies measure up, which ones are on the horizon, and how to identify patients who may be ideal candidates for the next generation of retinal disease therapies.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Discuss** current and future therapeutic agents for diabetic eye disease and neovascular age-related macular degeneration (nAMD), and the implications for patient outcomes
- **Identify** patients who may benefit from the next generation of retinal disease therapies
- **Develop** strategies to improve adoption of cutting-edge therapies for the treatment of diabetic eye diseases and nAMD into clinical practice

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PRETEST QUESTIONS

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

1. Please rate your confidence in your knowledge and ability to choose which patients in your practice may benefit from the next generation of durable retinal disease therapies (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. A 46-year-old patient with diabetic macular edema (DME) on monthly intravitreal aflibercept (2-mg dose) presents to your office for evaluation. She has done well on aflibercept and is happy with her vision. However, she is interested to see if she can extend the interval between her injections. She is currently unable to extend past 4 weeks due to reaccumulating cystic intraretinal fluid at the 4-week interval. Which of the following statements about future management options is TRUE?

a. Recent trials show evidence that high-dose aflibercept may help extend the treatment interval
b. Recent trials show evidence that high-dose aflibercept will not help extend the treatment interval
c. Recent trials show that high-dose aflibercept is inferior to 2-mg aflibercept
d. Recent trials have shown 10% of patients with DME are able to extend to 16-week dosing schedule with high-dose aflibercept

3. Which of the following emerging retinal treatments turns the eye into a "biofactory" to produce its own supply of anti-VEGF?

a. Intravitreal ADVM-022
b. Intravitreal brolucizumab
c. KSI-301
d. Intravitreal faricimab

4. A 45-year-old patient with diabetes mellitus presents to your office for evaluation. He has a history of center-involving DME and has received monthly injections of aflibercept for 6 months. He has had an incomplete response to aflibercept, and his OCT shows central cystic intraretinal fluid in both eyes. Which of the following is a reasonable treatment option for this patient?

a. Continue aflibercept therapy
b. Switch agents to faricimab
c. Consider treatment holiday
d. Panretinal photocoagulation

5. A 56-year-old patient with DME well controlled on monthly ranibizumab presents to your office for evaluation. She has a history of chronic uveitis. She is happy with her vision and treatment, however her monthly appointments have becoming increasingly difficult to coordinate with her work schedule. Which of the following is the most reasonable treatment option?

a. Discussion of implantation of the port delivery system with ranibizumab
b. Discussion of switching agents to faricimab
c. Discussion of switching agents to brolucizumab
d. Discussion of switching agents to bevacizumab

6. Which of the following suprachoroidal injection techniques will help minimize pain with injection?

a. Rapid injection pace
b. Slow injection pace
c. Slow needle entry followed by rapid injection pace
d. Rapid needle entry with rapid injection pace

Achieving New Heights of Durability in Retina: What's in Store for Retina Treatments and the Patients Who Need Them

We're all very familiar with intravitreal anti-VEGF treatments for retinal vascular diseases. What some of us may be less familiar with are the candidates on the runway, some of which leverage other modes of drug delivery. Most of these pipeline therapies aim to decrease the treatment burden by increasing treatment intervals – currently, an unmet need in retina. With safety being of paramount importance, these durable therapies introduce a new set of challenges for us to tackle.

This roundtable discussion addresses the advances in treatments, how we can incorporate them into the treatment paradigm along with the associated technical and practical considerations, as well as identifying those patients who may benefit and welcome greater durability of treatment.

– Nancy M. Holekamp, MD, Moderator

EMERGING THERAPIES IN RETINA

Q | **Dr. Holekamp:** Let's begin with a brief overview of emerging therapies, and their mechanisms of action and durability, starting with intravitreal delivery. It's tried and true, but there are some new drugs that utilize this delivery route. Dr. Wykoff, could you tell us about the clinical trial program for high-dose (8 mg) aflibercept?

Charles C. Wykoff, MD, PhD: The current FDA-approved dose is aflibercept 2 mg. But if the dose were increased 4-fold, could we achieve better visual, anatomic, or durability outcomes? Clinically, any of these could be valuable. We've seen two previous examples in which there were signals that increasing the anti-VEGF molar dose may be able to provide clinical value. First, the HARBOR trial demonstrated there may be some durability benefit, as the ranibizumab 2-mg arm required slightly fewer *pro re nata* (prn) doses than the ranibizumab 0.5-mg arm.[1] More recently, brolucizumab 6 mg demonstrated stronger drying capacity than brolucizumab 3 mg and aflibercept 2 mg.[2] These data suggest that increasing the molar anti-VEGF-binding capacity could translate into better outcomes.

The phase 2/3 PHOTON and phase 3 PULSAR trials, in diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD), respectively, compared three monthly doses of aflibercept 8 mg followed by 8q12 or 8q16 dosing, with three (PULSAR) or five (PHOTON) monthly doses of aflibercept 2 mg followed by 2q8 dosing.[3] Approximately 90% of patients with DME and around 80% of patients with nAMD achieved a 16-week dosing schedule, with no new safety signals compared to aflibercept 2 mg, and the higher dose was determined to be non-inferior to aflibercept 2 mg.[3]

Q | **Dr. Holekamp:** That was an excellent summary. Dr. Wolfe, can you comment on the KSI-301 clinical trial program?

Jeremy D. Wolfe, MD, MS: Most clinicians will be familiar with KSI-301, or tarcocimab tedromer, as an anti-VEGF conjugated to a biopolymer, which increases vitreal retention. Certainly, the early phase trials across several different retinal disease states demonstrated biological activity and positive results.

Unfortunately, the phase 2b/3 DAZZLE trial in nAMD didn't meet its primary endpoint of noninferiority compared to aflibercept 2q8 dosing.[4] There are several likely reasons for this but, from my point of view, the single greatest reason lies in the trial design. Participants were given three loading doses and then dosed no more frequently than every 3, 4, or 5 months. In the pursuit of demonstrating durability, efficacy was forfeited. We should note that their phase 3 BEACON trial in retinal vein occlusion did meet its primary endpoint of noninferiority in vision gains, while doubling the treatment interval.[5]

Q | **Dr. Holekamp:** Yes, the nAMD trial results were disappointing, and perhaps failed to account for some of our high anti-VEGF need patients who wouldn't be well served with q12w dosing. We're still waiting on the results of the phase 3 GLEAM and GLIMMER trials in DME.[6,7] Another intravitreal strategy that I'm particularly excited about is gene therapy. Dr. Weng, could you give us an overview?

Christina Y. Weng, MD, MBA: When we talk about reaching new heights in durability, gene therapy sets the highest bar. It's the ideal, potentially "one-and-done" treatment that leverages the concept of turning the eye into a "biofactory" where the patient's eye produces its own supply of anti-VEGF.

One intravitreal gene therapy candidate is ADVM-022, also known as ixoberogene soroparvovec (Ixo-vec), which is delivered intravitreally.[8] This delivery route has had limited success with prior gene therapies; however, Ixo-vec uses a modified adeno-associated viral (AAV) vector called AAV.7m8, which offers better penetration into retinal cells. It encodes for an aflibercept-like protein and is currently being evaluated in the phase 1 OPTIC

trial (n = 30). There are four cohorts, each given either high or low doses with oral or topical eyedrop prophylactic steroid regimens.[8] Of note, these patients were not treatment-naive and, in fact, have demonstrated a high anti-VEGF need. Overall, after a single dose of Ixo-vec, patients were able to maintain stable visual acuity and anatomic outcomes over 3 years. Most impressively, there was a dose-dependent 81% to 98% reduction in mean annualized anti-VEGF injections.[8] The phase 2 LUNA study is currently enrolling participants and will evaluate the low dose from the OPTIC trial as well as an even lower dose.[8] The rationale behind these dosing selections is, in part, related to findings from the phase 2 INFINITY study for DME, which was terminated early in April 2021 following a suspected unexpected serious adverse reaction (SUSAR) of hypotony and irreversible vision loss.[9] While gene therapy could be a promising treatment, we're still in its infancy and must be vigilant about safety and overall outcomes.

Q | **Dr. Holekamp:** I couldn't agree more. It has a long runway. There are still issues with intraocular inflammation (IOI) and pigmentary changes in the retina with other gene therapies, but it's certainly very exciting.
Moving onto surgical implantation approaches, as vitreoretinal surgeons, many of us welcome the fact that nAMD or DME could become surgical diseases. Dr. Wolfe, could you take us through the OTX-TKI program?

Dr. Wolfe: OTX-TKI is an intravitreal axitinib hydrogel implant and is a tyrosine kinase inhibitor (TKI). Historically, TKIs have been of great but unfulfilled interest in retina. That seems to be changing. There are several programs looking at TKIs now, and this implant is given as an injection. It's designed to have a duration of 3 to 6 months, and broadly inhibit pro-inflammatory and angiogenic factors. The interim 7-month data from the phase 1 trial demonstrated a favorable safety profile, and by month 7, 73% of subjects remained rescue-free.[10]

Q | **Dr. Holekamp:** The phase 1 data looked very good. As a pan-VEGF receptor blockade, TKIs are very desirable in retina, but tend to have some intraocular toxicity, and so must be packaged. As an aside, TKI drug names end in -nib and antibody names end in -mab.
Another TKI, EYP-1901 is an implant packaged with vorolanib. Dr. Weng, could you tell us about that program?

Dr. Weng: EYP-1901 utilizes the same delivery platform as the fluocinolone acetonide intravitreal implant sans the polyimide shell, which renders it bioerodible. A recent read-out of the phase 1 DAVIO trial at the American Society of Retina Specialists (ASRS) meeting showed a well-tolerated safety profile.[11] Patients with nAMD who received at least three anti-VEGF injections within the past 6 months were included; on average, patients had received eight injections in the prior year. There were four dose cohorts and patients were given a one-time dose of EYP-1901. At 6 and 12 months, there was an overall 79% and 74% reduction in treatment burden, and 53% and 35% remained supplemental injection-free, respectively.[11] Clinical trial programs for nAMD, retinal vein occlusion, and diabetic retinopathy (DR) are either under way or being planned.

Dr. Holekamp: In these early trials, the drying looks very impressive. But again, it's all about drug delivery because TKIs tend to be inflammatory.

Turning to suprachoroidal delivery, Dr. Wykoff, can you comment on the two different clinical trial programs in which its being used?

Dr. Wykoff: The first one is an axitinib injectable suspension, administered to the suprachoroidal space using a proprietary microinjector. Again, by being a pan-VEGF blocker, we may be able to achieve better visual and anatomic outcomes. It is currently in the dose-escalating phase 1/2 OASIS trial. The second is the gene therapy RGX-314, which produces a ranibizumab-like molecule. It is being evaluated in both subretinal and suprachoroidal programs, with the latter using a microinjector for both the nAMD and DR trials. Early reports are indicative of efficacy signals in both programs, with notably positive results in the ALTITUDE DR program.[12] While there was some ocular inflammation noted in both the nAMD and DR programs; more complete data is needed to guide the development of possible phase 3 trials.

Dr. Holekamp: There are also other companies developing their own suprachoroidal delivery systems, so we will see further exploitation of this space for drug delivery. What's interesting is that the choriocapillaris pores have a physiologic upper limit of 6 nm to 12 nm in size,[13] so any drug that's larger than this is well-retained in the suprachoroidal space. That makes it attractive for some of these TKI inhibitors that tend to crystallize and remain as depots even as the fluid gets absorbed. Viral particles are also larger than this pore size. The range of therapies suited to this space is exciting, but they do need to be validated in larger clinical trials.

PATIENT CONSIDERATIONS FOR EMERGING THERAPIES

Dr. Holekamp: There are so many therapies and modes of drug delivery in clinical development that are promising. However, as clinicians, we must consider which of our patients can benefit from these.

Dr. Weng: That's right. We are used to injectables and they are very accessible to patients, but have their limitations because of the required frequency of treatment for most. On the other hand, newer, more durable therapies also have advantages and drawbacks. We need to be deliberate in weighing out therapeutic options and considering the patient holistically. Elements that should be considered include their treatment frequency tolerance, personalized needs, and responses to current therapies.

For example, the port delivery system with ranibizumab (PDS) requires surgery, and some of the gene therapies require concurrent vitrectomy. Given that our patients with nAMD tend to be elderly, middle-ground durability agents such as the TKI implants

may be good options for those who are not ideal surgical candidates or simply do not prefer to undergo surgery but want better durability than that offered by our current injectables. There is no doubt that our treatment and decision-making algorithms will become more complex.

Dr. Holekamp: Absolutely. The bigger that toolbox gets, the longer the conversation with our patients. With these more durable treatments, I wonder whether we'll still require patients to show a response to anti-VEGF injections. Will we continue to use them as starting points and then gradually pivot to more durable options?

Dr. Wolfe: Great questions, and we may not have answers to those just yet. I believe intravitreal anti-VEGF injections are here to stay for a few reasons. One, it would be prudent to see responsiveness to anti-VEGF before committing patients to a higher risk procedure. Two, some insurance companies will require us to step through treatments anyway. Three, we already have patients on anti-VEGF that don't require frequent dosing. As the risk-benefit profile changes, we'll make changes as needed.

Dr. Holekamp: Certainly, a lot to figure out. There's also this phenomenon of tachyphylaxis, which may or may not become an issue when we switch patients to durable anti-VEGF therapy. What are your thoughts?

Dr. Wykoff: I have not seen evidence to suggest that tachyphylaxis is an important clinical issue. The very large majority of patients that I see who initially respond to anti-VEGF therapy continue to respond over time. In comparison, tachyphylaxis to anti-VEGF therapy would be a phenomenon in which the clinical response decreases over time. However, what we do see commonly in clinic is patients who are responders but need frequent dosing, and incomplete responders or patients in which the fluid doesn't completely resolve despite adequate anti-VEGF therapy, particularly in DME.

Dr. Weng: I agree. Depending on the study you read, tachyphylaxis occurs in up to 10% of patients,[14] although I cannot say that my own experience reflects this. In general, given the correct diagnosis, patients with nAMD are largely responsive to all anti-VEGF agents. A confounding issue in these studies is what qualifies as tachyphylaxis. Is it an incomplete response, completely absent response, or lack of response following some threshold of injections? This is not very well defined in our field. What I will say is that diseases can evolve over time and this, in itself, can lead to a lack of response. Additionally, different patients respond differently to different agents.

Q | **Dr. Holekamp:** Does switching help? What are the benefits of switching between anti-VEGF agents?

Dr. Wykoff: All of our current anti-VEGF agents, with the exception of brolucizumab, are broadly similar in their efficacy and safety profiles, with some apparent meaningful differences in drying capacity in some disease states. There are switching studies that can support any direction of switching.[15-19] If a patient is incompletely responsive to a specific agent, such as bevacizumab, I often switch them to aflibercept, which I have found to be a superior drying agent to achieve the maximal anatomic drying effect. If a patient is incompletely responsive or does not sustain a very durable response to aflibercept, I have been switching some of these patients to faricimab.

"Thinking about patient selection, I typically refer to clinical trials for general guidelines, particularly the inclusion and exclusion criteria."

—Nancy M. Holekamp, MD

Dr. Holekamp: Dr. Wolfe, do you ever switch to brolucizumab as a better drying agent than aflibercept?

Dr. Wolfe: I have previously; however, since the real-world reports of IOI, I no longer use brolucizumab. While I did see a positive drying effect in those handful of patients, I don't like the risk-benefit profile. Now that faricimab is available, I also switch to that for a better drying effect.

Dr. Holekamp: I agree, it's great to have choices for our incomplete responders. Inevitably, in the long-term, they will have variable responses to treatments. At the end of the day, continuing treatment, regardless of agent, is probably the best course of action.

Thinking about patient selection, I typically refer to clinical trials for general guidelines, particularly the inclusion and exclusion criteria. Some trials evaluated treatment-naïve patients and others evaluated known anti-VEGF responders. For example, the phase 3 TENAYA and LUCERNE trials for faricimab in nAMD included only treatment-naïve patients.[20] However, in practice, with new agents, we typically choose our most difficult patients to trial them. In contrast, the gene therapy trials have so far only included those with a known high anti-VEGF need. For intravitreal delivery, choosing patients is straightforward. However, with surgical options that promise a longer lasting treatment effect, how might we assess a patient's candidacy? Let's consider the PDS as an example; although, we should note there was a recent voluntary recall of the implant device. No implant procedures are currently being performed, but refill exchanges for patients who already have an implant, continue. Hopefully, this is a temporary pause.

Dr. Weng: With the PDS specifically, patient selection is a

measured consideration. While surgical treatment is unlikely to become a first-line option, the PDS may be beneficial for some. An ideal candidate would have demonstrated anti-VEGF responsiveness with a high anti-VEGF need and has healthy conjunctiva with few ocular comorbidities. We have learned that the conjunctiva plays a critical role in minimizing various risks associated with the PDS, specifically endophthalmitis, conjunctival retraction, and conjunctival erosion.[21]

Dr. Holekamp: I'd also add that it's important to take a good ocular history and identify a history of IOI, because any surgical procedure can trigger recurrent uveitis.

Dr. Wolfe: Any patient who has demonstrated a need for continuous anti-VEGF treatment over a long period of time, are surgically ideal candidates, and are open to the procedure are worth considering for long-lasting surgical options like the PDS. I even had a list of patients who had heard about the PDS and wanted it as soon as it was made available to us. On the other hand, there are others who make an occasion out of the monthly visit with their family member and don't want to give that up.

My belief is that continuous therapy is going to be superior. The data currently only supports that it is as effective as monthly treatments. However, with the degree of undertreatment we have in the real world, I believe continuous therapy in the long term will bear out as better than monthly treatment.

Q | **Dr. Holekamp:** You make a good point about patients self-selecting for some of these therapies based on their drivers, and even barriers, for treatment.
Let's then consider our recalcitrant cases. Dr. Wykoff, do you think that these new treatments will be more effective for these patients?

Dr. Wykoff: It will be highly individualized. For example, some eyes have a very robust response to anti-VEGF monotherapy, which wears off after a few weeks. They might be perfect candidates for gene therapy or longer lasting surgical options, like the PDS, when it hopefully becomes available again. If a patient with DME is an incomplete responder and needs combination therapy, they may also be an ideal candidate for this but continue to need additional steroid treatment.

Anti-VEGF injections are so highly effective and safe that the bar has been set very high. So far, the safety profile of these more durable options has been less than ideal. For example, I have had several long conversations about the PDS, but patients typically become hesitant when they hear about the black box warning and the possible need for additional surgeries for adverse events. If patients are doing well on injections and are happy with them, they often elect to continue with them in my clinic thus far.

Dr. Holekamp: You're right that we're having more frequent and longer conversations with patients to individualize their treatment. In that regard, patient buy-in is key, particularly with a surgical procedure like the PDS. I always begin by saying that it's a trip to the operating room (OR). Those who have had cataract surgery find it easier to understand the concept of an intraocular implant and outpatient surgery. They understand the need for postoperative visits and medication regimens. One of the most important things to mention is the postsurgical drop in vision. It's transient and vision generally recovers within 4 to 8 weeks, but it can be alarming for patients who aren't prepared for it.

"Anti-VEGF injections are so highly effective and safe that the bar has been set very high."

–Charles C. Wykoff, MD, PhD

Another aspect to discuss is that the PDS is designed to decrease the treatment burden, outside of those postoperative visits. The clinical trials portended the possibility of reduced treatment burden but didn't demonstrate it because subjects were required to attend monthly monitoring visits.[21] Monitoring will always be important and as clinicians, we'll have to discern new monitoring patterns for these more durable treatments. Again, patient buy-in is key, and we'll have to tailor those conversations so we can appropriately apply these newer tools.

INTEGRATING NOVEL, DURABLE THERAPIES INTO CLINICAL PRACTICE

Dr. Holekamp: Part of making these therapies available to our patients is understanding how to properly use them and integrate them seamlessly into our practice. As I previously mentioned, there is currently a voluntary recall of the PDS implant device, but we hope this is temporary and that surgical training for the implant will resume when (and if) it becomes available again. Dr. Weng, I believe you've been trained to perform the PDS procedure. Tell us a little about that.

Dr. Weng: Unless they were involved in the clinical trials, this is a new procedure for most surgeons. Having spoken to experienced colleagues and in becoming familiar with the technique myself, I do not think the technique is particularly difficult per se; however, what we have learned from each phase of the PDS clinical trials is that there are nuances to every step in the implantation of the PDS that can mitigate some of the risks previously mentioned. For example, at the beginning of the phase 2 LADDER trial, vitreous hemorrhage rates approximated 50%.[22] The procedure was updated to include laser ablation of the sclerotomy as the surgeon entered the vitreous cavity, which significantly reduced these rates to 5.1%.[22] Other nuances include meticulous closure of

the conjunctiva and even how to hold the refill-exchange needle during the refill exchange procedures. The latter may impact septum dislodgement, which has been observed recently in a small number of cases. Therefore, training is important.

The manufacturer has done a great job of onboarding surgeons wanting to perform the implantation. You start off with virtual learning – modules on their website that go step-by-step through the procedure. There are virtual lectures and peer-to-peer didactic discussions with another retinal surgeon who can take you through each step. The manufacturer will then send a surgical device specialist to work with you, hands-on, with modules and models. This specialist can also be present in the OR, for the first few implantations, to walk you through the procedure. Peer-to-peer education and sharing of best practices is going to be key in this space. As we get better at this technique, we'll see further mitigation of some of the risks we've observed so far.

Dr. Holekamp: I am so glad you mentioned septum dislocation, Dr. Weng. The manufacturer performed commercial testing of the implant, while looking into these cases, by simulating multiple refills and identified that the septum did not meet their standards.[23] Hence, the voluntary recall was issued. Dr. Wolfe, what's your experience with learning this procedure?

Dr. Wolfe: I was part of the clinical trials and have participated in the training several times to stay current. I would encourage everybody to take full advantage of the training resources afforded to you. There's also a virtual reality simulator, which is extremely valuable, that allows you to repeat each step and become comfortable with the motions.[24]

I'll emphasize that the sclerotomy for the PDS is different to other sclerotomies we perform. The first time I performed the procedure, the specialist in the OR was able to encourage me to push past the point I would have naturally stopped with other sclerotomies. This guidance, from someone who had observed a lot of procedures, was useful for me and my OR staff. Some surgeons may not be comfortable with strangers in their OR, but I would still welcome that help for as long as it's available to me.

Dr. Holekamp: The device specialist will also be present for the refill exchange procedures. They're a walking, talking volume of shared experiences and best practices from many surgeons, in various locations, and over many years. They're valuable assets in the OR, as you've both mentioned. Following these new surgical procedures to the letter is critical to avoid the complications identified in the phase 3 ARCHWAY trial.[21] This is additionally important because we only have the one pivotal trial in nAMD and are awaiting results from the PAVILION and PAGODA trials in DR and DME.[25,26] For example, applying laser ablation to the pars plana isn't routine in our clinical practice, so it does require training. Complications like conjunctival bleb leaks, retractions, or erosions, which were associated with endophthalmitis, can be directly related to missteps during the surgical procedure, eg, not identifying Tenon's capsule and the conjunctiva, and anchoring them with a scleral bite to the limbus.[27] Implant dislocations were associated with making scleral cuts greater than 3.5 mm. Overall, as we incorporate new treatments into our practice, particularly ones that require surgery, it's incredibly important to follow the instructions for use.

Q | **Dr. Holekamp:** Speaking of new devices, suprachoroidal injections will soon become a technique with which we'll all need to gain familiarity. Dr. Wykoff, are you currently using it in your practice?

Dr. Wykoff: Suprachoroidal injections have been discussed for nearly a decade, and of course, suprachoroidal delivery of a triamcinolone acetonide injectable suspension was recently FDA approved and is commercially available for the treatment of macular edema secondary to uveitis.[28,29] These administrations are performed in clinic. Unlike intravitreal injections where we inject into a real space, suprachoroidal injections expand a potential space. Because of that difference in anatomy, the injection is slower, ie, over 10 to 20 seconds. To maneuver the needle into the correct space, you dimple the conjunctiva and sclera, pushing firmly on the ocular surface, and inject slowly while holding the needle in place.[29] After the drug is injected, the needle is held in place for an additional 10 to 20 seconds to allow the injection volume to disperse posteriorly and circumferentially within the suprachoroidal space.[29] In addition to being validated in uveitis studies, the technique is also being used by other investigational agents in DR, nAMD, and choroidal melanoma trials.[12,30-32] I would encourage those who perform intravitreal injections to familiarize themselves with suprachoroidal injections because the procedure is here to stay and I think its use will increase over time as new therapies utilize this approach. It's also efficient to learn the technique and the manufacturer has a short virtual program to help with the learning curve.

Dr. Holekamp: Are there any potential complications?

Dr. Wykoff: The three key possible complications to consider are suprachoroidal hemorrhage, endophthalmitis, and pain, and only the third is clinically relevant at this time. In the early days of the technique, there was a worry of rupturing bridging blood vessels due to suprachoroidal space expansion, but I'm not aware of any such incidences over the thousands of injections that have now been performed. Similarly, there have been no reports of endophthalmitis following a suprachoroidal injection that I am aware of; although, all intraocular and periocular injections do carry this risk. Pain is a factor that has been mitigated as we as a field have become better at performing this procedure. As with intravitreal injections, some patients will be more sensitive to it. To minimize pain, I'd recommend injecting slowly (hence, slow expansion of the suprachoroidal space) and ensuring that you are entering the right space. Don't force the injection intrasclerally and dissect the scleral lamellae as this can cause pain. Inadvertent injections into the intravitreal, subretinal, or subconjunctival

regions are also a theoretical risk,[33,34] but relatively rare and notably uncommon with the shorter needles, ie, less than 1%.

Q | Dr. Holekamp: Thank you for those insights. A practical consideration with therapies that require fewer treatments, and we touched upon this earlier, is rethinking our monitoring strategies. Currently, I see my patients frequently and am comfortable with that. Are we concerned about less-than-adequate monitoring if our patients are further extended on their treatment regimens?

Dr. Wolfe: Yes, there is some concern, and for two main reasons: making sure the eye is being adequately treated and catching conversion to nAMD in the fellow eye. Often the patient isn't aware of the latter, but we'll catch it at an early stage when we perform optical coherence tomography (OCT) imaging. We all know that initiating treatment when baseline vision is good is one of the best predictors of maintaining good vision. While we do have technologies such as vision monitoring and home OCT that can help us in this regard, I don't think we're quite there yet. I'm hoping these technologies evolve relatively rapidly.

Dr. Weng: I agree that while it is beneficial to extend treatment intervals as much as possible, we could lose the ability to monitor their progress and fellow eye. As Dr. Wolfe noted, this is where home monitoring could have great applicability. However, even technologies like home OCT are not able to detect all complications. For example, in the case of PDS, it is important for patients to be monitored for conjunctival compromise or infection.[21] Treatment versus visit burden is always going to be a sticking point, and a balance of these should be considered, while prioritizing safety.

In considering complications that may manifest in the longer term, eg, macular atrophy, it becomes more complicated. The data are mixed regarding anti-VEGF therapy and macular atrophy, and it remains unknown how the pharmacokinetics of continuous delivery of anti-VEGF via the PDS or gene therapy may impact our understanding of this type of atrophy. Recently, a preplanned exploratory analysis of the LADDER trial showed that over a mean of 22.1 months, there was no apparent increase in the prevalence of macular atrophy with the PDS compared to monthly ranibizumab.[35] Of course, these investigations need to be performed in larger trials.

Dr. Wykoff: We don't want to sacrifice safety for durability. Until we better understand the safety profiles of newer therapies, it's prudent to see patients more frequently than risk missing potential issues. To that point, a lot of patients in the PDS programs are extremely happy, but some have come in with associated conjunctival problems that are asymptomatic. We can't completely rely solely on symptoms or even home OCT monitoring. With a device in the eye wall, these patients will need to be examined regularly.

Dr. Holekamp: Safety first; we've learned that repeatedly.

CASE 1: FREQUENT FLYER WITH STRICT INTERVALS

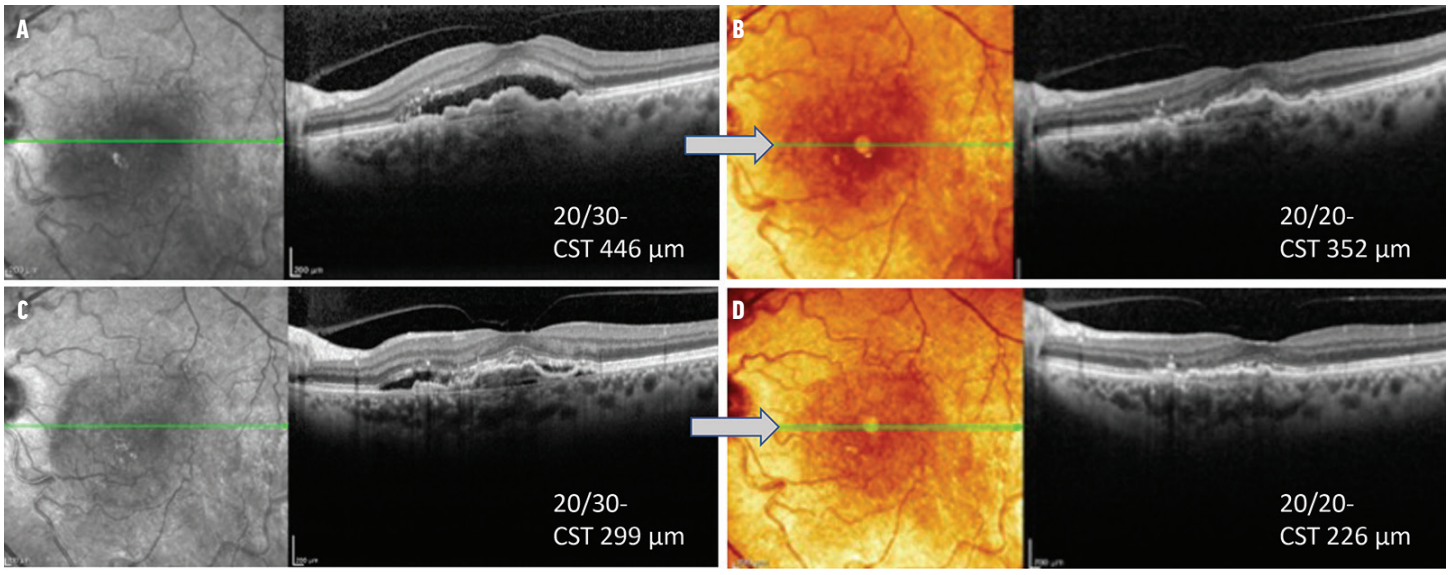
Dr. Weng: This case involves a 71-year-old woman with bilateral dry AMD who I have observed for several years. One day, she came in with blurry vision in her left eye (20/30-) and was diagnosed with conversion to nAMD (Figure 1A). She emphasizes the importance of patient education; because she was aware of the symptoms of nAMD, she presented early on before her vision was more significantly compromised. As Dr. Wolfe noted, that's probably the most important prognostic factor in how patients will fare on anti-VEGF therapy.

I started her on monthly anti-VEGF, and after three injections, her VA improved to 20/20 and the fluid resolved (Figure 1B). Once a patient is dry, I typically follow the treat-and-extend regimen and extended her to 6 weeks. However, after 6 weeks, there was fluid recurrence and VA dropped to 20/30 with subjective blurriness and metamorphopsia. I contracted her back to every 4 weeks and fluid completely resorbed with VA improving to 20/25+. I then decided to extend her to 5 weeks, to maximize her interval, but again, fluid recurred (Figure 1C). She was tightened back to 4 weeks and again, looked great (Figure 1D). Clearly, she responds well to anti-VEGF therapy, but requires a very strict monthly schedule and is someone many of us would refer to as a "frequent flyer," ie, a patient who is exquisitely sensitive to an every-4-week interval.

However, I know that she lives an hour away from my clinic and takes care of an ill family member. Compounding that, patients unfortunately face wait times at the clinic, so these q4w injections are a significant time burden for her and she struggles to consistently follow this schedule. Even though she appreciates it when her VA is 20/20, she sometimes has lapses in which she goes longer than 4 weeks between injections. We have talked about transferring her care to a clinic closer to home, but she feels comfortable with our practice. I tried switching her to a different anti-VEGF agent but saw no additional durability benefit.

She embodies the real-world challenges facing our high anti-VEGF need patients. We are in the process of bringing faricimab into our facility, and hope this may allow patients like her to extend their intervals.

Dr. Holekamp: We all have these patients, and again, they may be one of the reasons why the KSI-301 nAMD trial failed to meet its primary endpoint.[4] They also exist in DME. For example, between 10.8% and 13.3% of patients in the phase 3 YOSEMITE and RHINE trials for faricimab remained on q4w dosing through week 52, as their central subfield thickness didn't drop below 325 µm.[36] Your case would be an ideal candidate for the PDS, when it is available again, which was equivalent to monthly ranibizumab injections,[21] if she also had the other clinical characteristics that lend themselves toward a surgical procedure, ie, healthy conjunctiva, willingness to go to the OR, no other hardware in the eye (eg, scleral buckle or glaucoma valve), no history of uveitis, or severe dry eye.



Courtesy of Christina Y. Weng, MD, MBA.

Figure 1. Patient requiring strict monthly treatment. OCT image at presentation (A) and after three monthly anti-VEGF injections (B). Disease recurrence following an attempt to extend to a 5-week interval (C). Fluid resolution and vision improvement following immediate return to a 4-week interval. CST, central subfield thickness (D).

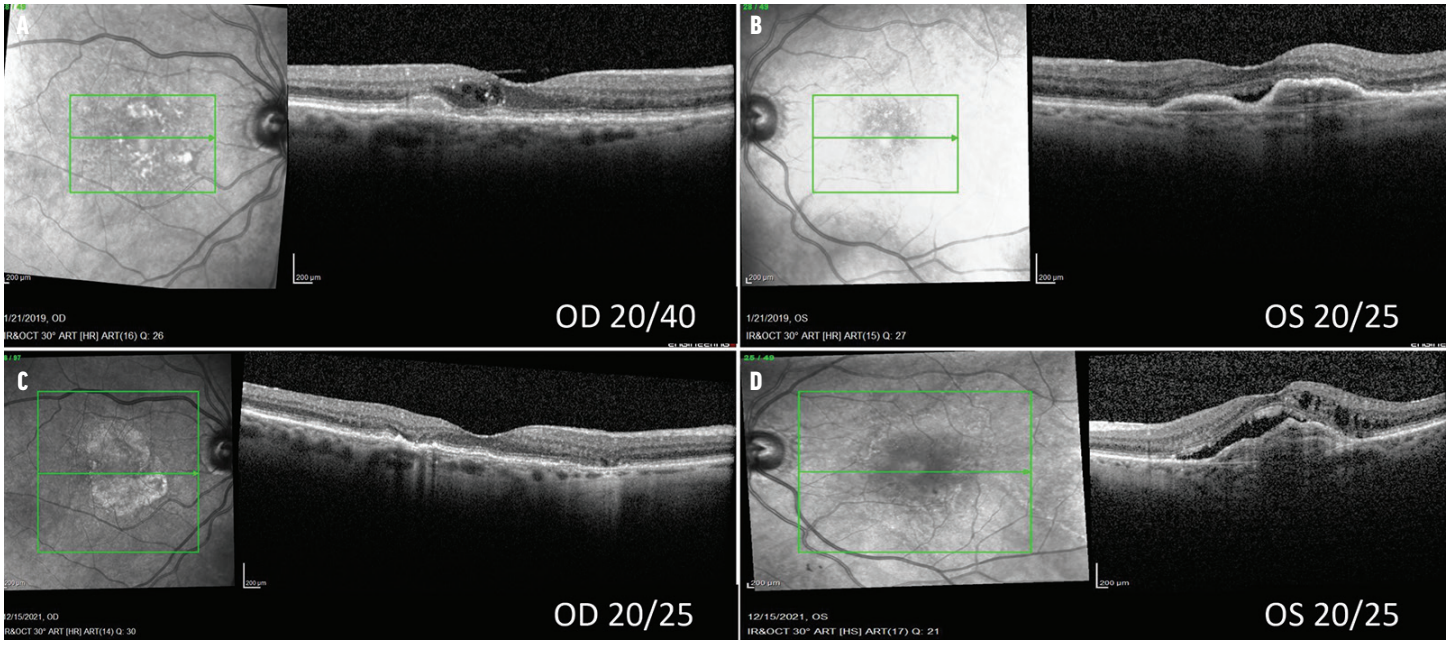
CASE 2: LONGER LASTING THERAPY OR MONTHLY INJECTIONS?

Dr. Holekamp: When this patient presented to me in 2016, she was 82 years old, and her VA was 20/20 in the right eye and 20/40 in the left eye. She began receiving bevacizumab injections for nAMD in the left eye. By January 2019, she'd received 22 anti-VEGF injections. At this time, she developed nAMD in the right eye (VA 20/40), with intraretinal cystic changes near the fovea, and even though the left eye had persistent subretinal fluid, it was doing well (VA 20/25; Figure 2A, B).

She became the first patient I enrolled into the ARCHWAY trial. She fulfilled the prerequisite of demonstrating a response to anti-VEGF injections after receiving three ranibizumab injections in the right eye, which then received the PDS. Per the study protocol, her left eye was switched to monthly ranibizumab.

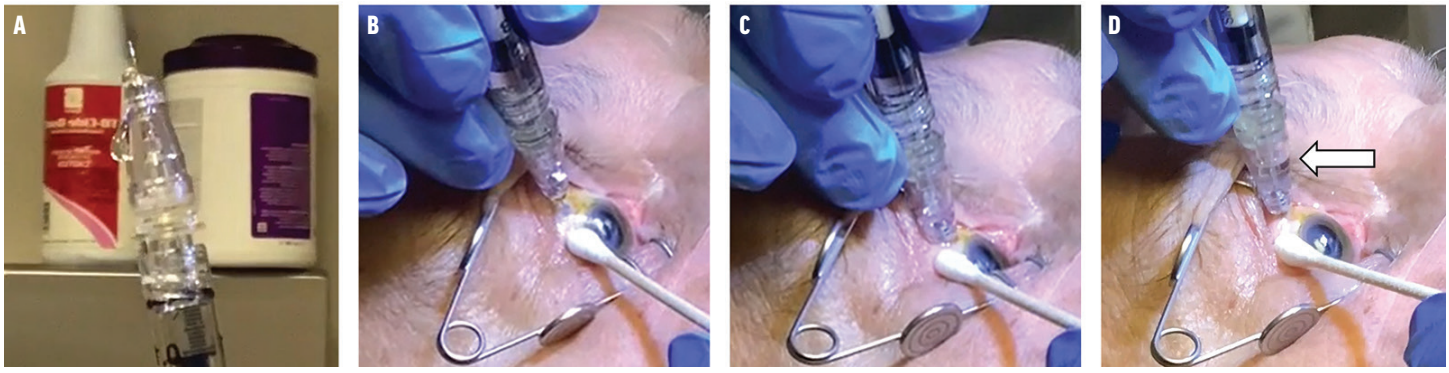
The patient didn't feel the implant under the conjunctiva. Of course, the septum can be seen when the eyelid is lifted and the release control element, which passively diffuses the high concentration of ranibizumab into the vitreous cavity, can also be seen if the patient looks up and to the left.[21] In primary gaze, you don't see the PDS.[21]

As of January 2022, she was 87 years old and her VA was 20/25 in both eyes, which is a good outcome but achieved in different



Courtesy of Nancy M. Holekamp, MD.

Figure 2. Patient with PDS in the right eye and monthly injections in the left eye. OCT images of right (A) and left eyes prior to PDS implantation (B). OCT images of right (C) and left eyes 3 years after PDS implantation (D).



Courtesy of Jeremy D. Wolfe, MD.

Figure 3. PDS refill exchange procedure. The refill needle is attached to a Luer-lock syringe and is primed without residual air (A). The volume for refill/exchange is 0.1 mL. After prepping the eye, the refill need is aligned with the device and centered on the septum (B). The septum is pierced, and the refill needle enters the device (C). The refill is completed as evidenced by reflux of fluid into the refill needle (D; arrow).

ways. The right eye had five in-office refill exchange procedures, and the left eye had 55 anti-VEGF injections. This patient was in the trial, so was very compliant, but clearly demonstrates that we can offer patients a choice between the PDS or regular anti-VEGF injections.

Dr. Wolfe: Did she express a desire to have the PDS implanted in her left eye?

Dr. Holekamp: We talked about it. However, she's now 88 years old and has had interceding health issues that prevent her from returning to the OR. She really likes the PDS in her right eye, and it isn't uncommon for trial subjects to want it in their fellow eye.[21] In December 2021, the right eye with the PDS was completely dry and the left eye was still wet and requiring monthly ranibizumab injections, but VA was 20/25 in both eyes (Figure 2C, D).

Dr. Wykoff: The pigment epithelial detachment in the left eye looks like it's becoming larger and there's more intraretinal fluid. She may be underdosed.

Dr. Holekamp: Yes, that is correct. These features support the need for continuous therapy, which may have some advantages over the pulsatile therapy that injections provide. However, we have yet to prove that. It's certainly intriguing to think about. Her disease has continued to progress over almost 6 years, but I wouldn't consider this tachyphylaxis to her anti-VEGF regimen. It is a disease changing over time as she gets older. Still, VA of 20/25 speaks to adequate disease control in the left eye.

CASE 3: PDS REFILL-EXCHANGE TIPS

Dr. Wolfe: Segueing nicely from Dr. Holekamp's case about PDS implantation, I wanted to go through the refill-exchange procedure (Figure 3). It can be tricky just as often as it can be easy, but it's certainly well within our capabilities.

First, it's important not to have any air bubbles, so make sure to express all of them. There's plenty of drug in the vial to allow for this. The refill needle is a clever technology. The dual lumen allows the exchange of residual fluid in the implant for fluid from the vial, to ensure that the implant is refilled with an almost pure concentration of ranibizumab. I use a lid speculum to ensure good exposure and place a drop of betadine to the implant location. Unlike a typical intravitreal injection, I tend to stand on the contralateral side to the PDS eye because it's a rigid implant and you must get the angle exactly right. If it isn't properly aligned, you'll run into the wall and potentially bend the needle. You know it's the right spot because, (1) you're able to enter, and (2), as you begin to fill the implant, you can see the fluid refluxing into the refill needle.

Dr. Weng: What anesthesia do you use for refill exchanges?

Dr. Wolfe: I use topical 4% lidocaine for all my injections.

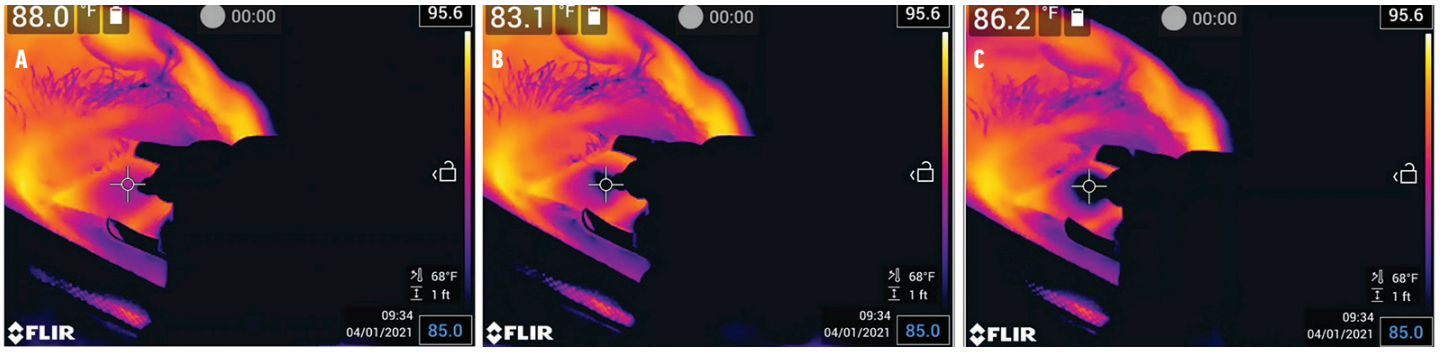
Dr. Holekamp: The total volume in the refill-exchange needle is 100 µL, with 80 µL used to flush out the existing volume and 20 µL to refill the PDS, which is enough drug to do a one-to-one volume exchange. As Dr. Wolfe noted, if you hit something hard, it's either the flange or the device. The septum is rubber, so you can feel the tactile difference. It's 1 mm in diameter and the refill exchange needle is almost 0.5 mm in diameter; there's very little room for error. You must cannulate it perpendicularly, and in the center, to be able to get through the thin neck of the implant.

Dr. Wolfe: That's probably how the septum dislocations are happening. Clinicians are entering the septum almost, but not entirely, perpendicularly, and go along the neck of the device and push the septum down. Being perpendicular to the implant is really important.

Dr. Holekamp: I agree. There's no amount of twisting or turning that will overcome malalignment. If you feel you aren't in the right spot, it's best to withdraw, pause, and try to enter the septum again.

Dr. Wolfe: Universally, patients who have the PDS in one eye and receive injections in the other eye prefer the refill procedures, even if we sometimes need a couple attempts to perform it. It may be because we aren't going through the sclera anymore.

Dr. Holekamp: They feel the pressure, but not pain.



Courtesy of Charles Wykoff, MD, PhD.

Figure 4. Suprachoroidal injection visualized by infrared thermal imaging. Warmer tones correspond to the scleral surface. Cooler tones correspond to the injected fluid. The white bullseye denotes the point of injection, which is centered over a growing blue spot (A-C).

CASE 4: PERFORMING SUPRACHOROIDAL INJECTIONS

Dr. Wykoff: One of the challenges with suprachoroidal injections, particularly in clinical trials, is making sure the fluid is being delivered into the correct space. We've previously shown that anterior segment OCT can evaluate the expansion of this potential space,[32] and so can ultrasound. We are currently using infrared thermal imaging in some clinical trials to do the same (Figure 4). Under infrared imaging, the sclera has warmer colors and the injected fluid (white bullseye in the images of Figure 4), which is cooler than body temperature, has cooler colors and can be seen expanding circumferentially and posteriorly around the eye. If you inject it into the subconjunctival space, or get reflux, it balls up around the injection side and does not form the expanding flat, circular pattern.

There's a discussion about whether infrared thermal imaging would be used clinically. For more expensive drugs, eg, gene therapy, we may want to be certain the drug is entering the right space.

We spoke earlier about the injection technique, but let's discuss the details. When we were first performing these suprachoroidal injections, we were using subconjunctival lidocaine for anesthesia due to concern for patient pain. Nowadays, however, most clinicians forego the subconjunctival injection in favor of topical anesthesia. I suggest starting with the shorter 900 µm needle, oriented perpendicular to the eye wall. Make sure to press firmly and create significant dimpling of the sclera. I like to use loupes or lighted readers to ensure a clear view of that dimpling effect. As mentioned previously, after the 10- to 20-second injection, hold the needle in place to prevent fluid egress. As you withdraw, use a cotton swab to tamponade the area of injection to minimize reflux.

Patients will feel pressure. Most of this comes from the actual needle and device hub being pushed on the eye wall, creating that dimpling effect. Some patients will feel a bit more pressure in the eye as the injection is delivered.

Q | Dr. Holekamp: Can you comment on the resistance that indicates you aren't in the right space?

Dr. Wykoff: That's a great point. With our current approach to suprachoroidal injection, it is critical to be absolutely perpendicular to the scleral surface and generate good dimpling. Because you're expanding a potential space, there will be a little resistance, but I believe any retina surgeon can readily differentiate that from a lot of resistance. The No. 1 take-home message is, if you feel like there is a lot of resistance, don't force it; the tip of your needle may be in the sclera and you do not want to force the injection into the sclera, which could dissect the scleral lamellae and be painful for the patient.

In this case, it's best to withdraw the needle and try again in the same area. If you're already in tangentially and then move to 90°, the needle may still take a longer path into the suprachoroidal space. Therefore, withdraw the needle and re-enter the sclera, taking care to be perpendicular to the surface. Usually if there's resistance, you aren't in far enough. If there is still substantial resistance with good dimpling and a 90° approach, switch to the longer needle. This is required in about 5% to 12% of eyes.

Dr. Weng: When you're injecting with a short needle, does the eye tend to roll?

Dr. Wykoff: That's a great question. There can be some movement, especially as the patient moves and looks around. Once you're engaged, pushing, and creating that dimple, there's minimal movement. You can also use a cotton swab to stabilize.

Dr. Holekamp: Thank you, that was a great case, and one that will be helpful as more and more novel therapies use the suprachoroidal delivery route. ■

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Expiration Date: December 2023

INSTRUCTIONS FOR 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/2206-2-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

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

Name _____ DOB (MM/DD) _____

Phone (required) _____ Email (required)* _____

Address/P.O. Box _____

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**Evolve does not share email addresses with third parties.*

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
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss current and future therapeutic agents for diabetic eye disease and neovascular age-related macular degeneration (nAMD), and the implications for patient outcomes	_____	_____	_____
Identify patients who may benefit from the next generation of retinal disease therapies	_____	_____	_____
Develop strategies to improve adoption of cutting-edge therapies for the treatment of diabetic eye diseases and nAMD into clinical practice	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your knowledge and ability to choose which patients in your practice may benefit from the next generation of durable retinal disease therapies (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. A 46-year-old patient with diabetic macular edema (DME) on monthly intravitreal aflibercept (2-mg dose) presents to your office for evaluation. She has done well on aflibercept and is happy with her vision. However, she is interested to see if she can extend the interval between her injections. She is currently unable to extend past 4 weeks due to reaccumulating cystic intraretinal fluid at the 4-week interval. Which of the following statements about future management options is TRUE?

a. Recent trials show evidence that high-dose aflibercept may help extend the treatment interval
b. Recent trials show evidence that high-dose aflibercept will not help extend the treatment interval
c. Recent trials show that high-dose aflibercept is inferior to 2-mg aflibercept
d. Recent trials have shown 10% of patients with DME are able to extend to 16-week dosing schedule with high-dose aflibercept

3. Which of the following emerging retinal treatments turns the eye into a "biofactory" to produce its own supply of anti-VEGF?

a. Intravitreal ADVM-022
b. Intravitreal brolucizumab
c. KSI-301
d. Intravitreal faricimab

4. A 45-year-old patient with diabetes mellitus presents to your office for evaluation. He has a history of center-involving DME and has received monthly injections of aflibercept for 6 months. He has had an incomplete response to aflibercept, and his OCT shows central cystic intraretinal fluid in both eyes. Which of the following is a reasonable treatment option for this patient?

a. Continue aflibercept therapy
b. Switch agents to faricimab
c. Consider treatment holiday
d. Panretinal photocoagulation

5. A 56-year-old patient with DME well controlled on monthly ranibizumab presents to your office for evaluation. She has a history of chronic uveitis. She is happy with her vision and treatment, however her monthly appointments have becoming increasingly difficult to coordinate with her work schedule. Which of the following is the most reasonable treatment option?

a. Discussion of implantation of the port delivery system with ranibizumab
b. Discussion of switching agents to faricimab
c. Discussion of switching agents to brolucizumab
d. Discussion of switching agents to bevacizumab

6. Which of the following suprachoroidal injection techniques will help minimize pain with injection?

a. Rapid injection pace
b. Slow injection pace
c. Slow needle entry followed by rapid injection pace
d. Rapid needle entry with rapid injection pace

ACTIVITY EVALUATION

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

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

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

This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____No

Probability of changing practice behavior based on this activity: ____High ____ Low ____No change needed

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

Change in pharmaceutical therapy ____
Change in nonpharmaceutical therapy ____
Change in diagnostic testing ____
Choice of treatment/management approach ____
Change in current practice for referral ____
Change in differential diagnosis ____
My practice has been reinforced ____
I do not plan to implement any new changes in practice ____

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

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

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

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

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

Additional comments:

_____

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

_____

_____