May/June 2022

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Exploring a New Era in Retinal Disease Treatments

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Distributed with
RT Retina Today

Release Date: May 2022
Expiration Date: June 2023

Exploring a New Era in Retinal Disease Treatments

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Content Source

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

Activity Description

The recent FDA approval of two new retinal disease therapies, combined with others in the pipeline, ushers in a new era for the treatment of neovascular AMD (nAMD) and diabetic macular edema. 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 that 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 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 neovascular AMD 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. What was a key finding of the YOSEMITE and RHINE trials?

a. The PDS implant delivered equivalent visual acuity gains compared to monthly ranibizumab
b. Faricimab delivered superior visual acuity gain compared to aflibercept
c. More than 50% of patients receiving faricimab could be extended to 16 weeks or more between injections
d. Faricimab treatment was associated with an increased risk of endophthalmitis compared to aflibercept

3. What are the treatment arms in the SHORE trial?

a. OPT-302 with ranibizumab versus ranibizumab alone versus ranibizumab with sham
b. OPT-302 with aflibercept versus aflibercept alone versus aflibercept with sham
c. PDS with ranibizumab 100 mg/mL versus monthly ranibizumab
d. One-time injection of RGX-314 versus vehicle

4. A 77-year-old woman presents to your office for evaluation for distortion in her left eye for 3 weeks. On OCT, you notice a new fibrovascular pigment epithelial detachment with subretinal fluid. Which of the following is the best treatment course for this patient?

a. Photodynamic therapy
b. Intravitreal corticosteroids
c. Intravitreal anti-VEGF treatment
d. Observation

5. A 58-year-old pseudophakic man with diabetic macular edema is being treated in your office with intravitreal ranibizumab. He previously had poor response to aflibercept. He is responding suboptimally to ranibizumab with persistent cystic intraretinal fluid in his macula despite 7 months of ranibizumab every 4 weeks. Which treatment option is the most reasonable for this patient?

a. Maintenance on intravitreal ranibizumab
b. Trial of intravitreal corticosteroids
c. Switch to intravitreal aflibercept
b. Switch to intravitreal bevacizumab

Exploring a New Era in Retinal Disease Treatments

With the recent FDA approval of two highly durable therapies for retinal disease, we have entered a new era for the treatment of neovascular AMD (nAMD) and diabetic macular edema (DME). Along with others in the pipeline, the new treatments are employing novel strategies: one targets an alternative pathogenetic pathway implicated in nAMD and diabetic eye disease, and the other utilizes a surgically implanted drug delivery device to provide continuous anti-VEGF therapy. What's incredibly exciting is the potential to reduce the enormous treatment burden for patients being treated with frequent anti-VEGF injections. As additional treatments evolve along these lines, we may see shifts in the treatment paradigm. To explore where we are headed, we've convened a roundtable of thought leaders in the field to discuss how current therapies measure up, which ones are on the horizon, and how to identify patients that may be ideal candidates for the next generation of retinal disease therapies.

– Nancy M. Holekamp, MD – Moderator

GO-TO THERAPIES FOR NAMD, DR, AND DME

Dr. Holekamp: Let's start by discussing nAMD and our current treatment options for these patients.

Jennifer I. Lim, MD: Right now, the go-to therapy for most physicians is probably off-label bevacizumab. As we know, bevacizumab was compared to ranibizumab in the CATT trial, in patients with nAMD, and was found to be equivalent, producing vision gains that were within 2 letters of ranibizumab at 1 year.[1] All things being equal, it's a reasonable drug with which to start treatment. The FDA-approved drugs are, ranibizumab, aflibercept, brolucizumab and most recently, faricimab. Compared to ranibizumab and bevacizumab, aflibercept has shown potential, in a few case series, to be more efficacious in eyes with pigment epithelial detachments (PED).[2-5] Brolucizumab, which was approved for nAMD in 2019, was superior to aflibercept in terms of drying;

however, there were rare complications of occlusive retinal vasculitis, which really limits its use.[6,7]

Q | Dr. Holekamp: Do these agents differ in their ability to improve vision?

Dr. Lim: With anti-VEGF, unfortunately, there's a ceiling effect. While vision gains do vary from trial to trial, the range is 7 to 11 letters.[8] There is a limit to what we can achieve; eyes that have worse initial baseline visual acuity have more potential to gain visual acuity and do so, as compared to eyes that have better visual acuity and thus, potentially fewer letters to gain (ceiling effect). The patient cohorts enrolled into these studies also differ slightly (baseline visual acuity, disease variations, and other factors), which can account for some of the differences we see. However, the bottom line is, visual acuity gains tend to be fairly uniform.

Dr. Holekamp: These four anti-VEGF monotherapies have some differences between them, but they don't really impact vision as much as we would like. Yes, brolucizumab had better drying in the phase 3 clinical trials when compared to aflibercept, in some circumstances, but then ran into a real-world problem of idiosyncratic intraocular inflammation (IOI).

Arshad M. Khanani, MD, MA: Yes, the main concern with brolucizumab is IOI and the rare events of irreversible vision loss with vasculitis and artery occlusion. In the real-world study we recently published, the rates of IOI and/or retinal artery occlusion was 2.4%, however, real-world data has its limitations.[9] In the phase 3 trials, the IOI rate was around 4%,[10] but the independent Safety Review Committee (SRC) found that it was closer to 4.6%.[7] Specifically, the rate of IOI and vasculitis was 3.3%, and IOI, vasculitis, and occlusion was 2.1%.[7] While it does happen early in most patients, the MERLIN trial, which assessed a monthly regimen in a non-naive population, found that it could happen any time.[11] That's why brolucizumab is not indicated for monthly dosing after the first three loading doses. We know this inflammation occurs because of an autoimmune response, but because we don't have a biomarker to predict which patients may be more susceptible, and the other anti-VEGFs are equivalent in terms of visual acuity, brolucizumab has become a second- or third-line agent.

Q | Dr. Holekamp: I agree. We may have a ranibizumab biosimilar this June. What do you make of it?

John W. Kitchens, MD: The FDA recently approved a ranibizumab biosimilar for nAMD, myopic choroidal neovascularization, and macular edema after retinal vascular occlusion.[12] The phase 3 study produced equivalent efficacy, and similar safety and immunogenicity profiles to traditional ranibizumab.[13] With any biosimilar, beyond safety and efficacy, we must think about what it might do to pricing. This could lead to a significant decrease in the pricing paradigm with which we are familiar.

"I want to note that biosimilars have a slightly different path to FDA approval compared to the reference molecule."

–Nancy M. Holekamp, MD

Dr. Holekamp: I want to note that biosimilars have a slightly different path to FDA approval compared to the reference molecule. Because they are chemically similar to the innovator molecule, far fewer patients are required for the approval trials, approximately 100. The primary endpoint is around 8 weeks, which equals only two doses of the biosimilar. However, for safety, these patients are followed out to 1 year. There may be some concerns around adoption–one is the price and what it does to the landscape–but the other is long-term safety, particularly given our recent experience with brolucizumab. There is a need for more education around the biosimilar approval process and what it means to be chemically equivalent.

Dr. Lim: I agree that pricing will be an issue, but safety is a big one. We know ranibizumab is extremely safe. We've been using it since 2006 and are very comfortable with it. With the biosimilars, I don't have that same comfort of safety. If I were going to start a patient on an anti-VEGF, I'd feel more comfortable using ranibizumab, with which we have had more than 15 years of experience, than the biosimilar. Additionally, there are other novel agents with extended durability that may become commercially available. They would be much more attractive choices, for me, over the biosimilar.

Dr. Kitchens: It may be that we won't get that choice. So often, insurance companies have dictated that we use bevacizumab off-label, and they may do the same here.

Dr. Lim: Unfortunately, we're experiencing that in the Midwest already. We have some insurers mandating a "fail-first" policy with bevacizumab. That is, a patient needs to fail at a trial of at least three bevacizumab treatments before receiving approval to use a branded drug. I would assume that the biosimilar is going to be more expensive than bevacizumab. Therefore, this might be another stepping stone, and the potential scenario could be bevacizumab first, then the biosimilar, then the branded agent.

Dr. Holekamp: Retina specialists do have an excellent comfort level with bevacizumab, and even though it's not FDA-approved for nAMD, it has an excellent price point. We may soon have a

bevacizumab, called ONS-5010, approved for ophthalmic indications. What do you think about this potential on-label bevacizumab?

Dr. Khanani: I agree with Drs. Kitchens and Lim. With new drugs on the horizon, it will be difficult for biosimilars or FDA-approved bevacizumab to be first-line therapies. However, I'm not impressed with the clinical trial because they compared monthly ONS-5010 to ranibizumab administered every three months in previously treated patients, which we know doesn't work for majority of the patients.[14] Yes, it'll likely get approval based on the trial data as we know bevacizumab works and is safe, but patients are looking for better, efficacious, and durable options, with durability being the key unmet need. As a physician, I'll always look to get my patients the best option regardless of the price. While it's good to have FDA-approved bevacizumab, if we have the right patients and assistance programs, I do my best to use branded agents. Bevacizumab is a great drug, but it won't move our field forward. My other concern is that the trials were done in nAMD. Once ONS-5010 is approved, what do we use to treat patients with DME and retinal vein occlusion (RVO)? Will we continue to require compounded bevacizumab for these patients? It'd become a complicated scenario.

Dr. Holekamp: Absolutely. The fact that the trial was done using the PIER protocol for ranibizumab does not instill confidence. The trial design drew a lot of criticism when the results were first released. It remains to be seen if ONS-5010 gets FDA approval and what it does to our access to "off-label" compounded bevacizumab.

Dr. Kitchens: The biggest unknown is "what will happen to compounded bevacizumab?" The guidance for human drug compounding outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act prohibits formulation of any medication that is FDA-approved in a compounding pharmacy.[15] It is possible that an FDA-approved version of bevacizumab specifically approved for ocular use may limit or eliminate access to the compounded form of the drug.

Dr. Holekamp: Thank you for that insight. I'm sorry to hear the news because all of us use bevacizumab on some proportion of patients and are comfortable with it. We'll stay tuned for these developments.

Let's consider the treatments used for diabetic retinopathy (DR) and DME. Here, we have a few more options besides anti-VEGF monotherapy including laser photocoagulation and intravitreal corticosteroids.

Dr. Lim: The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation could control macular edema, but only delivered 3 or more lines of improvement in about 15% of participants.[16] In some of the later protocols, this increased slightly. For that reason, most of us today wouldn't consider laser, except for two patient groups. The first would be eyes that have a defined area of microaneurysm within a circinate pattern that can be targeted by the laser without harming the perifoveal region and causing a scotoma. The second would be patients that are unable to attend regular anti-VEGF appointments.

We typically do use an anti-VEGF agent to treat DME, particularly for patients with relatively new macular edema. While you can try anti-VEGF in eyes with chronic DME, those eyes tend to have different cytokine profiles, ie, disease is less VEGF-mediated and more influenced by proinflammatory cytokines. Here, the fluocinolone acetonide or dexamethasone intravitreal steroid implants may be more efficacious. Although steroids are more efficacious in pseudophakic eyes with chronic DME, the risk of cataract formation or glaucoma development detracts from their use as primary treatment.

Overall, anti-VEGF are more broadly employed for DME treatment, ie, on-label ranibizumab and aflibercept and off-label bevacizumab. The DRCR.net PROTOCOL T study showed that all three agents are similarly effective when baseline VA is 20/50 or better.[17] The drying effect of the on-label agents may have been slightly better, but that didn't translate into a difference in visual acuity outcomes. However, when the VA was 20/50 or worse, aflibercept tended to do better in year 1, ranibizumab caught up to aflibercept by year 2, and both anti-VEGF drugs were better at drying the retina than bevacizumab.

Dr. Holekamp: I agree that anti-VEGF monotherapy is the mainstay of DME therapy, with laser being less favored and steroids restricted to a second-line approach because of the safety profile. What's emerging in this landscape is anti-VEGF therapy for DR.

Dr. Khanani: Based on the natural history of DR, patients with moderately severe or severe nonproliferative DR (NPDR)–level 47 to 53 in the ETDRS–have significant potential for disease progression over time.[18] Both ranibizumab and aflibercept are approved for treatment, and the data from the PANORAMA trial shows a promising decrease in the rate of vision-threatening complications (VTCs).[19] However, it's challenging to convince patients to have continuing treatment. These patients may *see* their disease on clinical imaging, but if they still have 20/20 VA, they may not *feel* it, unless they progress to proliferative DR (PDR) or DME. Certainly, agents with greater durability, eg, sustained-delivery platforms, may address this issue; however, for now, long-term usage of anti-VEGF agents in this patient population is very low.

Dr. Kitchens: It's very interesting: both PANORAMA and PROTOCOL W had similar results, but the conclusions were somewhat disparate. In PANORAMA, they concluded that aflibercept could reduce VTCs by up to 80%, used as infrequently as quarterly or four-monthly dosing. PROTOCOL W, on the other hand, acknowledged that aflibercept decreased the risk of VTCs, and indeed was a good treatment for DME and PDR, but was not necessary as prophylaxis because if these VTCs occurred, we had effective therapies for them.

"Faricimab inhibits both VEGF-A and Ang-2 and the TENAYA/LUCERNE trials have shown us that more than 70% of patients were extended to at least 12 weeks."

—Arshad M. Khanani, MD, MA

Dr. Holekamp: This is an emerging field; there are conflicting messages and practice patterns might vary widely, but they do trend toward monitoring closely and treating if complications occur. We might even be more proactive treating moderately severe or severe NPDR in the fellow eye of a patient who has already lost vision.

Dr. Lim: With PROTOCOL W, even though there was no visual acuity difference at 2 years, we are cautiously awaiting the 4-year follow-up results, which will reveal what happens with PRN treatments. If we see a visual acuity difference between the groups at 4 years, that will drive treatment usage.

NEXT GENERATION OF RETINAL DISEASE THERAPIES

Brolucizumab and High-Dose Aflibercept

Q | **Dr. Holekamp:** Data from the KITE, KESTREL, and KINGFISHER clinical trials evaluating brolucizumab in patients with DME was released during the past year. What does that data look like?

Dr. Kitchens: We were originally involved in the KINGFISHER study but pulled out when we found out about the inflammatory issues in brolucizumab-treated patients with nAMD. Fortunately, we never had vascular occlusive events but did have five cases of IOI. While I cannot speak to the visual acuity improvements in the clinical trial, I know the risk of inflammation was equivalent to that observed in the nAMD studies, with a higher rate in patients receiving monthly injections.[20] I do not foresee brolucizumab having a major role in DME.

Dr. Holekamp: The brolucizumab studies really drive home this point: "safety first, efficacy second." I agree with you. I'm unsure it will receive FDA approval and if it does, there may be low enthusiasm for brolucizumab in the DR/DME market, primarily because we have other options. We also have high-dose aflibercept that is currently in phase 3 clinical trials.

Dr. Khanani: My question is, can aflibercept 8 mg produce better durability and drying in patients with nAMD or DME? The data from the phase 3 PULSAR and PHOTON trials may be available later this year; however, data from the phase 2 CANDELA study in nAMD was presented at the 2022 Angiogenesis, Exudation, and Degeneration Meeting. Compared to aflibercept 2 mg, aflibercept 8 mg had no concerns of additional IOI. There was a trend toward better drying with aflibercept 8 mg, but this was not statistically significant. We saw similar trends for visual acuity with mean 7.9-letter and 5.1-letter improvements in the 8-mg and 2-mg groups, respectively, from baseline. We must be careful in making any meaningful conclusions because of the small number of participants. I'm looking forward to data from both the nAMD and DME phase 3 trials.

Moreover, what does the data need to show for us to adopt aflibercept 8 mg? Faricimab inhibits both VEGF-A and Ang-2 and the TENAYA/LUCERNE trials have shown us that more than 70% of patients were extended to at least 12 weeks.[21] Faricimab has set a high bar for aflibercept 8 mg and for widespread usage, aflibercept 8 mg must show comparable efficacy and safety.

Dr. Kitchens: We went through the high-dosing approach with ranibizumab years ago with the HARBOR and READ-3 studies and saw no significant differences.[22-24] Do we really think that a higher dose of aflibercept is going to yield anything more than what we saw with a higher dose of ranibizumab?

Dr. Holekamp: Aflibercept 2 mg and ranibizumab 0.5 mg work very well for 95% of patients. In a clinical trial that takes all comers, I'm dubious that we'll see differences in the mean best-corrected visual acuity (BCVA) change that will be enough for FDA approval. However, in my opinion and in our clinical experience, we may see the benefit of a higher dose in a very small subset of patients with a very high anti-VEGF need. It might give us longer durability and keep them dry for longer.

Dr. Khanani: The question is, what is the regulatory endpoint for the approval of aflibercept 8 mg? Is it anatomy or vision? In the HARBOR trial, vision was comparable between 0.5 mg and 2 mg ranibizumab; with a possible trend toward better flattening of PEDs and maybe better fluid resolution.[25] How will the regulatory endpoint gauge superiority of aflibercept 8 mg, beyond just better drying in a subset of patients?

Faricimab

Dr. Holekamp: Let's talk about another new therapeutic approach: faricimab. This is not just an anti-VEGF drug. Perhaps we could start by discussing the mechanism of action of faricimab.

Dr. Lim: Faricimab is a bispecific antibody targeting VEGF as well as angiopoietin-2 (Ang-2) and was recently approved for nAMD and DME. The Tie-2 receptor is involved in angiogenesis, and Ang-1 is an agonist of Tie-2, which stabilizes the vasculature.[26] Elevated Ang-2 blocks the effect of Ang-1 on the Tie-2 receptor and therefore, potentiates angiogenesis. Essentially, faricimab is a "one-two hit" of both the VEGF and Tie-2 receptor pathways. In addition, theoretically, faricimab also offers both an antiangiogenic

function and, because Tie-2 is involved in inflammation, an anti-inflammatory function.[26]

Q | **Dr. Holekamp:** It's more than anti-VEGF monotherapy, it's anti-VEGF 2.0. It's our first foray into targeting a second pathway in both nAMD and DME. How has faricimab played out in clinical trials for nAMD?

Dr. Kitchens: Quite nicely. The phase 2 STAIRWAY study[26] informed the dosing regimens used in the phase 3 TENAYA and LUCERNE trials. They compared faricimab 6 mg, loaded at four monthly doses, to aflibercept administered at three monthly loading doses followed by 8-weekly injections. With faricimab, they had variable dosing, ie, a personalized treatment interval (PTI) that depended on disease activity, where you could go every 8, 12, or 16 weeks between doses.[27] At the end of 1 year, the number of patients who could be pushed out to at least 16 weeks was nearly 45%, with more than 70% of patients extended to at least 12 weeks.[21] It seems to have impressive durability. During the first 3 to 4 months, faricimab had a greater drying effect compared to aflibercept. Although this was not statistically significant, it was better at all time points. We may get a "wow" effect from this new offering.

Dr. Holekamp: I'd like to point out that the visual acuity results were comparable between faricimab and aflibercept. I think this speaks to the ceiling effect. With these retinal diseases, it's less about the drug than it is about the point at which we start treating patients.

Dr. Kitchens: That is a great point. People may be a bit surprised by the lack of 2 lines of visual acuity improvement; however, this study enrolled patients with at least 20/32 VA. This is an important difference from previous studies, in which the BCVA on enrolment was usually 20/40. As we had a reasonable number of patients with good vision, it's not completely surprising that they only gained 5 or 6 letters.

Dr. Holekamp: True. What about faricimab for patients with DME?

Dr. Khanani: The phase 3 YOSEMITE and RHINE trials were based on learnings from the phase 2 BOULEVARD trial.[28] In the phase 3 trials, two faricimab arms were compared with on-label aflibercept. Patients treated with aflibercept received five loading doses followed by q8w dosing. The first faricimab arm—six monthly loading doses of faricimab 6 mg followed by fixed q8w dosing—was designed to see whether faricimab could achieve superiority in vision.[29] Six loading doses was chosen based on learnings from the BOULEVARD trial. The second arm was the PTI regimen—a standardized treat-and-extend. Patients received four loading doses and were then extended. Although monthly faricimab delivered superior visual acuity gains in the phase 2 trial compared to monthly ranibizumab,[28] it was noninferior to aflibercept in the phase 3 trials, with VA gains of 10 to 11 letters.[30] There was meaningful durability with more than 50% of patients extending to at least 16 weeks and more than 70% extending to at least 12 weeks. There was no safety signal that was not comparable to aflibercept.[30]

Q | **Dr. Holekamp:** I want to reinforce the finding that there was no superiority in visual acuity. However, in the matched phase of the loading doses, faricimab had better drying than aflibercept.[30] In addition, we've not seen this level of durability with other injectables for treating DME. In fact, the 2-year findings recently reported at the 2022 Angiogenesis Meeting saw 78% of patients achieving intervals of at least 12 weeks. It's remarkable. Faricimab has recently become commercially available. What are your thoughts on how to use it?

Dr. Lim: Patients who have shown a need for high-frequency treatment, for example monthly anti-VEGF injections, are going to be the initial patients on which I use faricimab. I am curious to see if I can get extended durability to reduce the number of injections. It's a great new drug to have in our armamentarium, and the fact that 50% of patients can be extended to 4 months is awesome. There's no other drug that can do that. Even if you look at the brolucizumab data, it does not come close to that—after 1 year, they achieved more than 50% of patients every 12 weeks,[20,31] but with faricimab we have 50% every 16 weeks.[30] Another important consideration with faricimab is there have been no cases of retinal vasculitis and IOI was not significantly different from aflibercept. Hopefully, we won't see inflammatory reactions when it is used in the real world.

Dr. Kitchens: I want to establish how faricimab works on patients with whom I'm more familiar. Diabetes is a great disease state in which to compare drugs. The DRCR.net Protocol T trial showed a difference in anti-VEGF therapies, and we may also see a difference with faricimab compared to other agents in our diabetic patients. I'm looking for patients who have persistent edema despite monthly injections. I'll switch them to faricimab and see if we can achieve an enhanced drying effect with longer durability, which may result in some improvement in visual acuity. In general, I will be trying it in previously treated patients.

OPT-302

Q | **Dr. Holekamp:** Let's discuss a couple of other drugs on the horizon. Perhaps we'll discuss OPT-302 next. What is their approach?

Dr. Khanani: OPT-302 inhibits VEGF isoforms C and D, with the idea that combined VEGF inhibition may produce better visual acuity outcomes. Their phase 2b nAMD trial showed that high-dose OPT-302 in combination with ranibizumab provided a significant 3.4-letter gain compared to ranibizumab alone. That led to the design of the pivotal SHORE and COAST studies, which are ongoing. In SHORE, the comparator and combination treatment are ranibizumab, and in COAST, it's aflibercept. It would be

exciting if this new mechanism of action shows us that we can go beyond anti-VEGF monotherapy in nAMD. But, what about treatment burden? Will patients need double the number of injections more frequently because of the benefit? These phase 3 trials should tell us more.

Dr. Holekamp: Dr. Gemmy Cheung from Singapore recently presented a subgroup analysis of OPT-302 in cases of polypoidal choroidal vasculopathy (PCV) at the 2022 Angiogenesis Meeting. It was provocative to see that pan-VEGF suppression could potentially lead to better outcomes in patients with PCV. Although, these are still early studies, they're very exciting and there's more to come.

Let's turn our attention to KSI-301 and its strategy for treating retinal disease.

KSI-301

Dr. Kitchens: It's a unique product–it's an anti-VEGF bound to a biopolymer conjugate. This extends the intraocular half-life of the drug. It's a very viscous drug and takes time to draw up into the needle. We give about double the normal dose, volume-wise, of other anti-VEGF agents and it must be injected through a thin-walled 27-gauge needle. We're in the clinical studies and it does seem like it has extended durability. In the phase 2 studies, the drug was able to last, on average, 4 months in patients with DME, nAMD, and retinal vein occlusion (RVO). In fact, the RVO results are the most impressive because, in my experience, these patients are one of the hardest to extend beyond a few months. In general, the enthusiasm around KSI-301 has waned a bit as the results of the phase 2b/3 nAMD study showed that only 60% of patients could be maintained on a 5-month dosing interval after three monthly loading doses.[32] This was a lofty goal, and one likely result of such a lofty goal, as Q5 month dosing resulted in lower visual acuity than the control group, which received aflibercept every other month.

Dr. Holekamp: It's interesting to see the strategies used to increase durability–KSI-301 has a very large size, whereas brolucizumab took the opposite approach, ie, a very small molecule but higher molar dose. However, this durability does not necessarily translate to vision gain.

What's really exciting and what I want to talk about is a completely new direction for treating patients with nAMD, DME, and DR: the port delivery system (PDS), a device, containing ranibizumab, that is surgically implanted and then refilled.

PDS

Dr. Kitchens: The PDS was recently approved for nAMD treatment, based on the phase 3 ARCHWAY study. The device is inserted through the pars plana, located superotemporally, and is implanted 4 mm back from the surgical limbus. It's covered by Tenon capsule and conjunctiva; there's no scleral patch graft like in glaucoma. The device is filled with a special concentration of ranibizumab, which passively diffuses into the vitreous. What I like about this device is that potential future therapies could be used in it, so that it's not just relegated to ranibizumab. The ARCHWAY trial design was based on the phase 2 LADDER study, which was a dose-escalating study that settled on ranibizumab 100 mg/mL. LADDER also had open-ended refills, meaning the device was filled at the time of implantation, patients were followed, and refills performed upon active exudation. The median time to refill was 15.8 months.[33] This indicates that we may see greater than a 6-month durability of treatment effect.

"More than 90% of patients, who had previously received intravitreal injections, reported a preference for the [PDS] over monthly injections."

–John W. Kitchens, MD

In the ARCHWAY study, patients received six-monthly refills of ranibizumab 100 mg/mL. The results showed equivalency to monthly ranibizumab, with fewer than 2% of patients requiring additional therapy prior to the 6-month mark, which is unbelievable.[34] More than 90% of patients, who had previously received intravitreal injections, reported a preference for the implant over monthly injections. The only caveat with the PDS, borne out in LADDER and ARCHWAY, are the potential surgical complications, including risks of vitreous hemorrhage, bleb formation, hypotony, and inflammation. There is also a risk for endophthalmitis, almost 2%, which was most concerning to us and the FDA.[34] All of these cases occurred more than a month after device implantation and were precipitated by exposure of the implant through conjunctival recession or erosion over the implant surface. It will be very important to monitor these patients postoperatively, beyond the first few weeks, to ensure we don't see infection. Obviously, we would also discuss this increased risk, compared to intravitreal injections, with our patients.

Dr. Holekamp: The 96-week follow-up was presented at the 2022 Angiogenesis Meeting. What's impressive is that the anatomical and visual acuity results for the PDS were clinically equivalent to monthly intravitreal ranibizumab, which has been a gold standard for more than 15 years. The PDS could be a real game-changer in clinical practice. We know that clinical trial results don't match real-world data and vision in the real world declines over time. It will be interesting to collect real-world data on the PDS to see whether long-term vision results will be better in our patients.

Dr. Lim: We must remember that the patients in these studies had previously received anti-VEGF therapy–at least three

"The phase 3 PAGODA and PAVILION studies are evaluating the PDS in eyes with DME and moderately severe to severe NPDR, respectively."

—Jennifer I. Lim, MD

treatments within the first 6 months of screening.[33] If I'm treating a patient with nAMD with the PDS, I would select one who requires frequent anti-VEGF injections. However, I wouldn't immediately switch the patient to the PDS. If I could extend the patient to 2-month intervals, I might then try a drug like faricimab to push the interval to 3 to 4 months before trying the PDS implant.

Dr. Holekamp: In fact, on average, patients in the ARCHWAY nAMD trial had five anti-VEGF injections prior to undergoing surgery for the PDS. Thus, the PDS is not going to be an option for treatment-naïve patients but rather those with a high anti-VEGF need. The PDS is currently also being trialed in DR and DME, but results aren't yet available.

Dr. Lim: The phase 3 PAGODA and PAVILION studies are evaluating the PDS in eyes with DME and moderately severe to severe NPDR, respectively. To be enrolled in either study, patients had to have received at least two ranibizumab injections. Patients are scheduled for 6-monthly and 9-monthly refills in PAGODA and PAVILION, respectively.

Dr. Holekamp: It will be very interesting to see the safety profile in this group of patients with diabetes and compare it to patients with nAMD.

Dr. Lim: I would be a bit hesitant to implant the PDS in a patient with NPDR. If it was just to drive back the Diabetic Retinopathy Severity Scale (DRSS) level, Protocol W showed us there was no effect on visual acuity.

Dr. Holekamp: Excellent point. We'll have to wait for the trial data in this patient population.

It's great to see our field not only looking at different types of drugs, but also different types of drug delivery. I think strategizing around drug delivery will become a big part of what we do; it won't only be about the drug but also the delivery system. In that vein, we're going to turn our attention to suprachoroidal delivery.

Suprachoroidal Delivery

Dr. Khanani: It's an exciting new space. The suprachoroidal delivery of triamcinolone acetonide injectable suspension for the treatment of uveitis-associated macular edema was recently approved. What's more exciting is that we can inject tyrosine kinase inhibitors or even gene therapy like RGX-314, which is an AAV encoding a ranibizumab-like protein. I'm quite impressed with the data from the phase 2 ALTITUDE study for RGX-314 in DR with center-involving DME. The 6-month results, presented at the 2022 Angiogenesis Meeting, showed that more than 40% of patients achieved a 2-step improvement, similar to that seen in PANORAMA, meaning a one-time injection may be on par with frequent intravitreal injections. The suprachoroidal space itself is very exciting but we're still figuring out whether it's good for gene therapy, and of course, keeping an eye on safety.

Q | **Dr. Holekamp:** I'm curious about the reported issues of IOI for gene therapies in general. Did they see much at all in ALTITUDE?

Dr. Khanani: That's a good point. There were no cases of IOI in the data that was recently presented, but there were a few cases of episcleritis at the injection location, which did resolve. We're still learning about the cause of episcleritis and are keeping a close eye on IOI as we escalate the dose in the next cohort. In the phase 2 AAVIATE study in nAMD, there were a few patients with IOI that resolved within weeks of topical steroid administration. An important point here is that there's no prophylactic steroid regimen like with intravitreal gene therapy, for which we've used either oral or topical steroids. While we do expect some inflammation, the cases reported so far are mild and resolve with steroids. So far, we have not seen chronic inflammation but, of course, the numbers are still small, and we are continuing to learn more about safety.

Dr. Holekamp: Have you administered any suprachoroidal injections?

Dr. Kitchens: We were involved in an early RVO study for the suprachoroidal steroid therapy and did a couple injections. We were a little taken aback by the discomfort experienced by some patients. You need to inject it very slowly. In some people, the large bolus in the suprachoroidal space seems to hurt. We were also involved in a pluripotent stem cell study that used a suprachoroidal approach with a 37-gauge nitinol needle to penetrate externally into the subretinal space.

The cell suspension was injected subretinally, but on occasion, it was injected into the suprachoroidal space in animals and humans. Since we couldn't find any evidence of the cells in the suprachoroidal space, I'm frankly surprised there was as much uptake with RGX-314.

Dr. Holekamp: I was recently trained in suprachoroidal delivery. While I haven't executed it in any patients myself, I have to say the suprachoroidal space is a potential space. If it expands too quickly, patients will have pain, so your point for a slow injection is well taken. It's also different from intravitreal injections, where it's easy to see where the drug is going, so I question how we

might confirm the drug is in the suprachoroidal space. There will be a learning curve for us to become comfortable with this new mechanism of delivery.

CASE 1: MONTHLY ANTI-VEGF INJECTIONS: HOW TO EASE THE TREATMENT BURDEN

Dr. Lim: Our first case is a 73-year-old woman with bilateral nAMD and a history of breast cancer. She requires frequent injections. In 2004, her right eye had a choroidal neovascular membrane (CNVM) that led to a disciform scar, leading to count fingers vision. Her left eye developed choroidal neovascularization (CNV) in 2005, and eventually, an RPE rip. She presented to me in 2014, complaining of decreased vision and metamorphopsia in the left eye. She had extensive intraretinal fluid (IRF), a large PED, and evidence of an RPE rip, with 20/200 VA in the left eye (Figure 1).

She had received six prior anti-VEGF injections and I administered the next several aflibercept injections. During the course of 2015, her VA decreased to 20/400 due to a cataract. She underwent cataract surgery and VA improved to 20/50; however, she still had subretinal fluid (SRF) and IRF, and persistent CNV. She continued to receive monthly injections and her VA improved to 20/40, but the pathology remained. By December 2016, VA was 20/40, after a total of 27 aflibercept, and a bevacizumab treatment. OCT-A showed persistent CNV.

By 2018, her VA ranged from 20/60 to 20/100, depending upon the CNVM activity; however, by 2019, her VA range had narrowed to 20/50 to 20/60. In February 2022, her VA was 20/60 after a total of 72 aflibercept treatments. She still had some mild IRF and a PED, with active CNV (Figure 2). Because her other eye has a disciform scar, she's extremely motivated and comes in every month for treatment. She's been offered treatment with the PDS or faricimab.

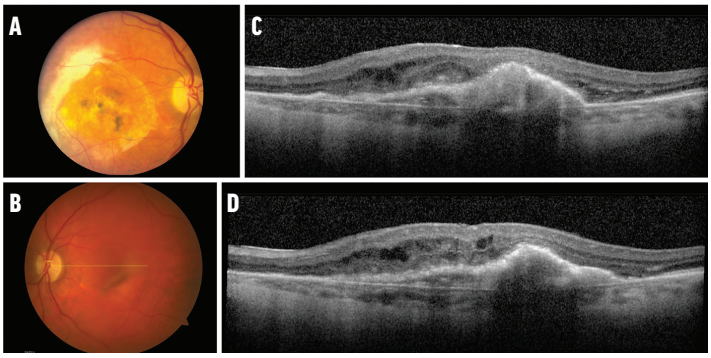

Figure 1: (A, B) Presenting fundus photographs of a patient with bilateral nAMD: disciform scar in the right eye and CNV with PED and RPE rip in the left eye. (C, D) Presenting OCT images of the left eye showing intraretinal fluid, subretinal fluid, PED, and CNV in the left eye. *Courtesy of Jennifer I. Lim, MD*

Dr. Holekamp: In between injections, the intraretinal and SRF goes away, correct?

Dr. Lim: Yes, she responds, and her vision improves, but not completely because of the PED component. When I've tried to extend her over the last few years, her vision declines, and the retina swells. She's happy and willing to come in every month and doesn't want to do anything drastic. She was hesitant about getting a surgical implant in her only seeing eye, and since she is doing well on frequent injections, she has decided on faricimab. We're trying to get it on formulary and see how she does.

Dr. Holekamp: Thank you, Dr. Lim. That was a great case.

CASE 2: THE PROMISE AND PERILS OF THE PDS

Dr. Kitchens: This case involves the first patient to receive the PDS implant post-approval. She was initially referred to us with low, broad PED, but in 2016, her VA dropped to 20/40. She

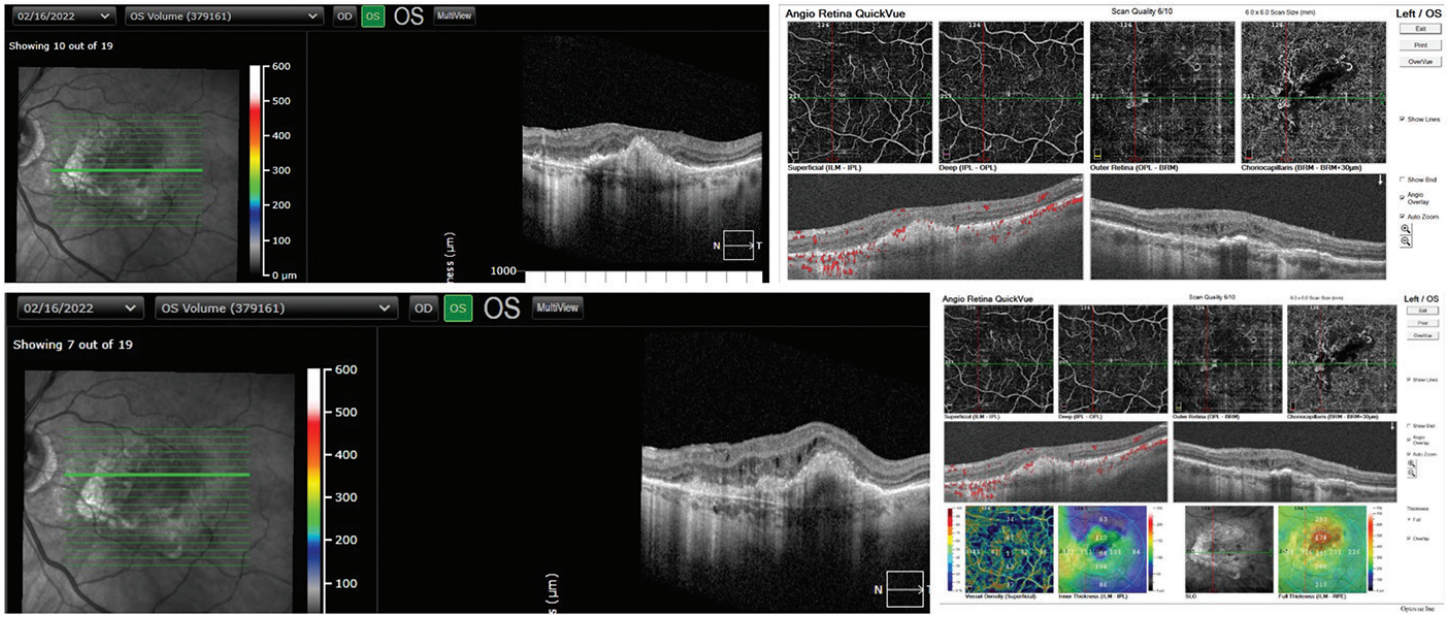

Figure 2: Most recent OCT and OCT-A images of a patient after 72 aflibercept injections. *Courtesy of Jennifer I. Lim, MD*

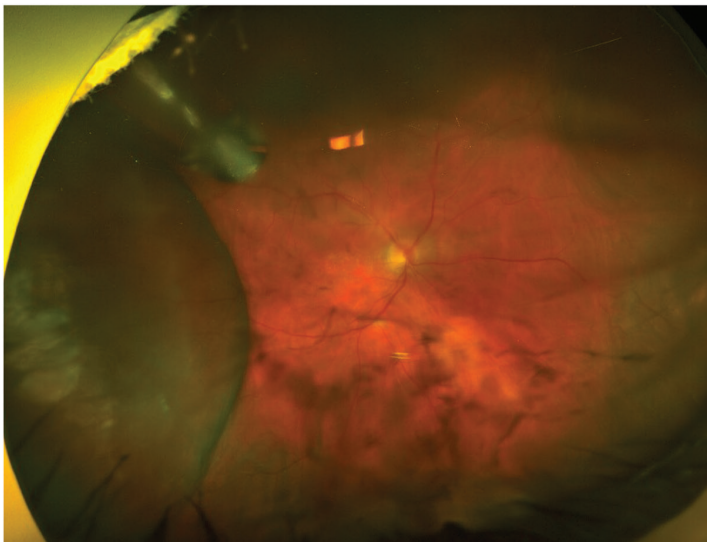

Figure 3: Postoperative day 1 complication of temporal serous choroidal detachment after PDS implantation. ***Courtesy of John W. Kitchens, MD***

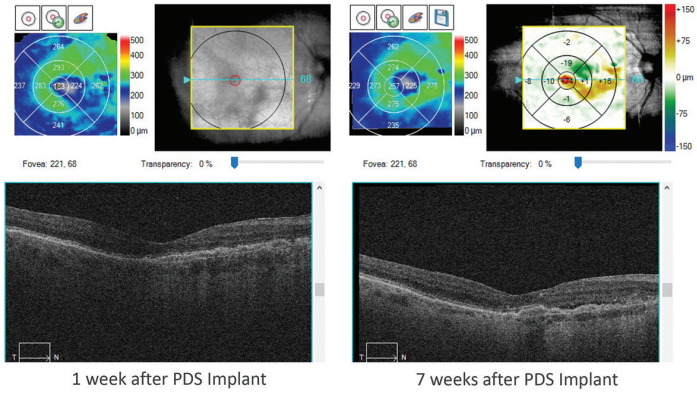

Figure 4: OCT images, showing recurrence of subretinal fluid, 7 weeks after PDS implantation. ***Courtesy of John W. Kitchens, MD***

developed distortion in her right eye and a fine area of SRF on OCT. The fluorescein angiogram showed a late leaking occult membrane. We started her on aflibercept, and she did well; however, during the next couple of years, every time we tried to extend her beyond 5 to 6 weeks, she would develop new SRF and be symptomatic. We had talked about the PDS implant months ahead of approval, and she was very interested in it as she had one good eye. This is key–while you're becoming familiar with the implant and refining your surgical technique, it's best to choose patients who aren't monocular due to the increased risk of infections and/or other complications.

In anticipation of the surgery, she received an aflibercept injection 2 weeks prior, and underwent uncomplicated placement of the implant. I went through a learning curve with the surgery during the clinical trials. After placing more than a dozen implants, I now feel more confident. I don't rush through them. I'm very careful about suturing. We also erred on the side of a smaller incision; a hair smaller than 3.5 mm.

On postoperative day 1, her VA was 20/60, with an intraocular pressure (IOP) of 4 mm Hg and a large temporal serous choroidal detachment due to the hypotony (Figure 3). As we had not encountered this in the clinical study at our site, I was a little nervous. She didn't have a conjunctival bleb or leakage around the implant, and in fact, the conjunctiva was covering it very nicely. She did have a bit of cell in the anterior chamber, so I started her on difluprednate and an antibiotic ointment four times a day.

On postoperative day 3, her IOP increased to 8 mm Hg. She could still see the choroidal in her peripheral vision and had some inflammation but was back to a preoperative VA of 20/50. Amazingly, her OCT images during this visit showed a much drier retina than she's had in the last couple years. The intraretinal edema was drier and we weren't expecting this to improve because it wasn't true cystic edema, just more thickening. By postoperative day 8, her IOP was 15 mm Hg, the choroidal was almost completely resolved and her VA was 20/25. She also noted an improvement in her visual acuity because she could now see the clock in her kitchen from her living room, which she hadn't been able to do in 2 years. Because the hypotony was better, we also tapered the steroids and stopped the antibiotic ointment.

When I saw her in January 2022, 7 weeks after the surgery, she was beginning to have recurrence of SRF (Figure 4); however, she was still seeing well, so didn't want to have an early refill or injection. When she returned in early March, the fluid had resolved, and her VA was 20/40.

This case brings up several interesting points. In the real world, in choosing patients who have received anti-VEGF injections for 4 to 5 years, we're choosing the toughest to treat. We may see some improvement in their vision with this sustained delivery; however, we may also see an early recurrence 3 to 4 months after implantation. We just do not know how these "frequent flyers" will respond to PDS and if it will provide the same type of durability we saw in the clinical trials, as these patients were not included in the studies.

With any new surgical procedure, there will be some surprises in the intraoperative or postoperative period. With the serous choroidal near the implant, I was certainly worried about how close the implant was to the retina and whether she might need surgery. However, cooler heads prevailed and sure enough, it did improve. It's about getting familiar and comfortable with the procedure, and not over-reacting to unusual findings, while also realizing what is concerning and needs to be addressed. For example, in this patient, I had to resist the urge to take her back to the operating room early on to see if there was a "leak" around the device. I had to trust that the incision was properly sized and not too large. The fact there was not a bleb over the device was also reassuring.

Dr. Holekamp: This is a great case. I recently did three PDS implantations and I did have hypotony early in the postoperative period with one of them. I was reminded by a glaucoma colleague that they poke holes in the eye all the time to purposefully lower the IOP, and the body's protective mechanisms keep closing those

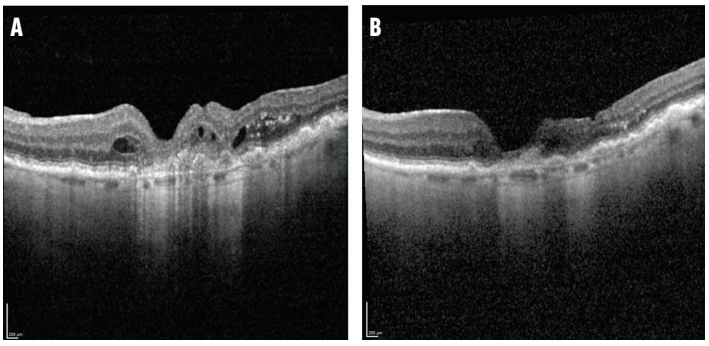

Figure 5: (A) OCT image showing intraretinal fluid 6 weeks after aflibercept administration. (B) OCT image showing no nAMD disease activity 7 weeks after faricimab administration. *Courtesy of Arshad M. Khanani, MD, MA*

holes. With observation, a low level of activity, and time, these things resolve on their own.

Regarding the recurrence of fluid, the ARCHWAY trial had very liberal supplemental treatment criteria–they wouldn't retreat based on the small amount of SRF you saw in this case. The ARCHWAY data didn't show cases of severe vision loss from undertreatment or persistent SRF, which makes us think differently about continuous versus pulsatile delivery of anti-VEGF. Maybe there's something protective about controlling the disease with continuous therapy rather than periodic injections.

Dr. Khanani: This was a great case highlighting the potential of sustained delivery to deliver visual acuity gain. We currently don't have real-world data for patients on aflibercept switching to the PDS. The phase 4 BELVEDERE study, which is ongoing, is assessing patient response to the PDS after treatment with either bevacizumab or aflibercept. At this point, I don't choose high-need patients for PDS, but rather those whose disease is well controlled. However, you can always administer supplemental injections after implantation if you feel disease activity will return.

CASE 3: FARICIMAB TREATMENT OF A VITRECTOMIZED EYE

Dr. Khanani: We've been following this 88-year-old female with bilateral nAMD for a while. The nAMD is more long standing in the right eye than the left. She initially had vitreomacular traction in the left eye and required a vitrectomy but was otherwise fine. She then developed nAMD in that eye in January 2021 and has since been on aflibercept. She lives out of town and cannot come in every month. While we do see her every 6 weeks or so, she still has IRF at these intervals (Figure 5A). She received her first faricimab injection on Feb. 14, 2022, and followed-up approximately 7 weeks later. Her OCT was completely dry with no disease activity (Figure 5B), highlighting the durability of faricimab compared to aflibercept.

Dr. Holekamp: Faricimab became available on Feb. 14, 2022, and you treated this patient on the same day. These are outstanding results already. Thank you all for this insightful discussion. ■

1. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*.2012;119(7):1388-1398.
2. Major Jr JC, Wykoff CC, Croft DE, et al. Aflibercept for pigment epithelial detachment for previously treated neovascular age-related macular degeneration. *Can J Ophthalmol*. 2015;50(5):373-377.
3. De Massougnes S, Dirani A, Ambresin A, Decugis D, Marchionno L, Mantel I. Pigment epithelial detachment response to aflibercept in neovascular age-related macular degeneration refractory to ranibizumab: time course and drug effects. *Retina*. 2016;36(5):881-888.
4. Tyagi P, Juma Z, Hor YK, Scott NW, Ionean A, Santiago C. Clinical response of pigment epithelial detachment associated with neovascular age-related macular degeneration in switching treatment from Ranibizumab to Aflibercept. *BMC Ophthalmol*. 2018;18(1):1-8.
5. Chan CK, Sarraf D, Abraham P, et al. Meticulous multimodal analysis of aflibercept therapy for submacular vascularized pigment epithelial detachment associated with neovascular AMD in a prospective case series, the EVEN study. *Am J Ophthalmol Case Rep*. 2020;20:100916.
6. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128(1):89-99.
7. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion–related events with brolucizumab: post hoc review of HAWK and HARRIER. *Ophthalmology*. 2021;128(7):1050-1059.
8. Dugel PU, Hillenkamp J, Sivaprasad S, et al. Baseline visual acuity strongly predicts visual acuity gain in patients with diabetic macular edema following anti-vascular endothelial growth factor treatment across trials. *Clin Ophthalmol*. 2016;10:1103-1110.
9. Khanani AM, Zarbin MA, Barakat MR, et al. Safety outcomes of brolucizumab in neovascular age-related macular degeneration: results from the IRIS Registry and Komodo Healthcare Map. *JAMA Ophthalmol*. 2022;140(1):20-28.
10. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84.
11. Khanani AM, Jaffe GJ, Wykoff CC, et al. Results from the phase 3a trial of brolucizumab in patients with nAMD and persistent retinal fluid. Presented at: American Academy of Ophthalmology; Nov 12-15, 2021; New Orleans, LO.
12. U.S. Food & Drug Administration. September 17, 2021. Accessed March 2, 2022. www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treat-macular-degeneration-disease-and-other-eye-conditions.
13. Woo SJ, Veith M, Hamouz J, et al. Efficacy and safety of a proposed ranibizumab biosimilar product vs a reference ranibizumab product for patients with neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2021;139(1):68–76.
14. Sharma A, Kumar N, Parachuri N, Loewenstein A, Bandello F, Kuppermann BD. On label bevacizumab for retina: where it stands. *Eye*. 2022:1-2.
15. Food and Drug Administration. Mixing, diluting, or repackaging biological products outside the scope of an approved biologics license application – Guidance for industry. Jan 2018. https://www.fda.gov/files/drugs/published/Mixing--Diluting--or-Repackaging-Biological-Products-Outside-the-Scope-of-an-Approved-Biologics-License-Application.pdf.
16. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: early treatment diabetic retinopathy Study report no. 4. *Int Ophthalmol Clin*. 1987;27(4):265-272.
17. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.
18. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991;98(5 suppl):823-833.
19. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: Results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol*. 2021;139(9):946-955.
20. Brown DM, Emanuelli A, Bandello F, et al. KESTREL and KITE: 52-week results from two phase III pivotal trials of brolucizumab for diabetic macular edema. *Am J Ophthalmol*. 2022;S0002-9394(22)00006-X.
21. Heier JS, Khanani AM, Ruiz CQ, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399(10326):19-25.
22. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046-1056.
23. Do DV, Sepah YJ, Boyer D, et al. Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes–Protocol 3 with high dose). *Eye*. 2015;29(12):1538-1544.
24. Sepah YJ, Sadiq MA, Boyer D, et al. Twenty-four–month outcomes of the ranibizumab for edema of the macula in diabetes–protocol 3 with high dose (READ-3) study. *Ophthalmology*. 2016;123(12):2581-2587.
25. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. *Ophthalmology*. 2016;123(10):2213-2224.
26. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):964-972.
27. Khanani AM, Guymer RH, Basu K, et al. TENAYA and LUCERNE: rationale and design for the phase 3 clinical trials of faricimab for neovascular age-related macular degeneration. *Ophthalmol Sci*. 2021;1(4):100076.
28. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*. 2019;126(8):1155-1170.
29. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical trials of faricimab for diabetic macular edema: study design and rationale. *Ophthalmol Sci*. 2021;2(1):100111.
30. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*. 2022;399(10326):741-755.
31. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84.
32. Kodiak Sciences. Kodiak Sciences announces top-line results from its initial phase 2b/3 study of KSI-301 in patients with neovascular (wet) age-related macular degeneration. Feb 2022. https://ir.kodiak.com/news-releases/news-release-details/kodiak-sciences-announces-top-line-results-its-initial-phase-2b3.
33. Khanani AM, Callanan D, Dreyer R, et al. End-of-study results for the ladder phase 2 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2021;5(8):775-787.
34. Holekamp NM, Campochiaro PA, Chang MA, et al. Archway randomized phase 3 trial of the port delivery system with Ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2022;129(3):295-307.

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___ 6-10
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___ <1

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___ 1-15
___ 16-30
___ 31-50
____ >50

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___ 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 AMD, 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 neovascular AMD 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. What was a key finding of the YOSEMITE and RHINE trials?

a. The PDS implant delivered equivalent visual acuity gains compared to monthly ranibizumab
b. Faricimab delivered superior visual acuity gain compared to aflibercept
c. More than 50% of patients receiving faricimab could be extended to 16 weeks or more between injections
d. Faricimab treatment was associated with an increased risk of endophthalmitis compared to aflibercept

3. What are the treatment arms in the SHORE trial?

a. OPT-302 with ranibizumab versus ranibizumab alone versus ranibizumab with sham
b. OPT-302 with aflibercept versus aflibercept alone versus aflibercept with sham
c. PDS with ranibizumab 100 mg/mL versus monthly ranibizumab
d. One-time injection of RGX-314 versus vehicle

4. A 77-year-old woman presents to your office for evaluation for distortion in her left eye for 3 weeks. On OCT, you notice a new fibrovascular pigment epithelial detachment with subretinal fluid. Which of the following is the best treatment course for this patient?

a. Photodynamic therapy
b. Intravitreal corticosteroids
c. Intravitreal anti-VEGF treatment
d. Observation

5. A 58-year-old pseudophakic man with diabetic macular edema is being treated in your office with intravitreal ranibizumab. He previously had poor response to aflibercept. He is responding suboptimally to ranibizumab with persistent cystic intraretinal fluid in his macula despite 7 months of ranibizumab every 4 weeks. Which treatment option is the most reasonable for this patient?

a. Maintenance on intravitreal ranibizumab
b. Trial of intravitreal corticosteroids
c. Switch to intravitreal aflibercept
b. Switch to intravitreal bevacizumab

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:

_____

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

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

_____

_____