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RT Retina Today

HOW TREATMENTS FOR DR/DME ARE MODERNIZING MEDICAL RETINA

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How Treatments for DR/DME are Modernizing Medical Retina

CONTENT SOURCE

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

ACTIVITY DESCRIPTION

This supplement summarizes an in-depth discussion into the available treatment options for diabetic retinopathy (DR) and diabetic macular edema (DME), as well as the challenges faced by retina specialists and patients in the current environment of COVID-19. The faculty also reviews emerging therapies and the potential they have for longer duration and improved outcomes.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists.

LEARNING OBJECTIVES

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

- **Describe** the pros and cons of current therapy options for diabetic eye disease
- **Articulate** the challenges facing retina specialists related to the complexities of managing patients with DR and DME
- **Assess** pipeline candidates under investigation for these patient populations

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DIGITAL EDITION

This supplement is part of a full curriculum, including video case discussions, available at: https://evolvemeded.com/course-group/modernizing-medical-retina-review-of-the-pipeline.

To view the online version of this supplement, go to http://evolvemeded.com/course/2127-2supp.

PRETEST QUESTIONS

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY EVALUATION/ SATISFACTION MEASURES FOR CME CREDIT.

1. Please rate your confidence in your ability to implement individualized patient treatment plans to ensure optimal outcomes for patients (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. Please rate your confidence in your ability to identify the relationships between retinal disease characteristics, drug, treatment frequency, visual and anatomic outcomes (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

3. A new patient presents for a diabetic eye exam. He is 45-year-old male with poorly controlled type 2 diabetes (HbA1c of 11%). His VA is 20/60 OU. There is some evidence of center-involved diabetic macular edema (DME) and questionable neovascularization in the far temporal periphery. In addition to OCT, what imaging is recommended for this patient?

a. Fluorescein angiogram
b. Ultra-widefield fluorescein angiogram
c. Indocyanine green angiography
d. Fundus autofluorescence

4. You confirm the patient from question 3 has center-involved DME, intraretinal hemorrhages in all four quadrants, but no NV. What is the recommended first-line therapy for this patient?

a. Intravitreal steroids
b. Subtenon steroids
c. Anti-VEGF injections
d. Focal laser

5. According to the RISE and RIDE extension studies, what percent of patients with DME will maintain visual gains and not require further anti-VEGF injections for 2 years with as-needed therapy?

a. 25 - 30%
b. 50 - 60%
c. 40 - 45%
d. 10 - 15%

6. What are some common reasons clinical trial outcomes do not translate to the real-world setting? Select all that apply.

a. Patients in the real-world have competing appointments and multiple comorbidities and are more likely to be lost to follow-up
b. Patients are followed for longer periods in clinical trials compared to the real-world setting
c. Ethnic minorities are over-represented in clinical trials, which makes it difficult to apply clinical trial data to real-world patient populations
d. Acuity measurements in the real world are different from those in clinical trials

7. Based on top-line results from YOSEMITE and RHINE, faricimab has shown a lasting durability of up to _____.

a. 14 weeks
b. 8 weeks
c. 16 weeks
d. 12 weeks

8. The INFINITY trial of ADVM-022 (AAV.7m8-aflibercept) in patients with DME was halted because _____.

a. Some patients developed occlusive vasculitis
b. Some patients developed hypotony and uveitis
c. There was no improvement in visual acuity
d. There was no improvement seen in DME severity

9. _____ is a gene therapy currently in development for diabetic retinopathy.

a. ADVM-022
b. RGX-314
c. OPT-302
d. KSI-301

10. Which statement regarding OPT-302 is accurate?

a. OPT-302 is a molecule that blocks VEGF-A and angiopoietin-2
b. OPT-302 is a molecule that blocks VEGF-C and VEGF-D and may be used in conjunction with an anti-VEGF-A agent
c. OPT-302 is a surgically implanted device that could significantly reduce the treatment burden for patients with DME
d. OPT-302 should be used to treat primarily patients with DME and VA of at least 20/25

How Treatments for DR/DME are Modernizing Medical Retina

Nearly 600 million people worldwide will be living with diabetes by 2030;[1] 33% of these patients will develop diabetic retinopathy (DR), and 11% will develop diabetic macular edema (DME).[2-4] Today's medical therapies can effectively treat DME and DR, and timely treatment can reduce the risk for severe vision loss by 90%.[5] Intravitreal anti-VEGF agents have become a mainstay of treatment for diabetic eye disease, and are currently the most commonly performed ophthalmic procedure.[5-29] Still, opportunities to address challenges like undertreatment, treatment adherence, and incomplete response remain. Several new therapies with novel mechanisms of action are currently being investigated in clinical trials, and some of these may be able to offer longer durability that could ultimately improve patient outcomes. The experts on this panel discuss what may be coming down the pike, how real-world data has driven the evolution of DME/DR treatments, and how to apply study findings to our own patient populations.

— Christina Y. Weng, MD, MBA, Program Chair

Dr. Weng: About 700 million people worldwide will have diabetes by 2045, and many of these people will be impacted by DR or DME.[2] Nearly all patients with type 1 diabetes and more than half of patients with type 2 diabetes will be affected by DR in their lifetime; anywhere from one-quarter to one-third of patients with diabetes will be develop DME.[30-33]

In the United States, approximately 500,000 people have clinically significant DME, and approximately 700,000 have proliferative DR (PDR).[34] DR is a leading cause of blindness and visual impairment in working-age Americans; in the United States, PDR causes 12,000 to 24,000 new cases of blindness annually.[15] The ophthalmic community must identify the most effective and efficient ways of treating diabetic eye disease. Despite the availability of very effective anti-VEGF treatments, eyes with PDR are 4 times more likely to develop sustained blindness after 2 years versus those with mild nonproliferative diabetic retinopathy (NPDR).[35] Ongoing challenges include patients who have incomplete responses or suboptimal visual outcomes.

CURRENT TREATMENTS AND THERAPIES FOR DME AND DR

Q | Dr. Weng: Let's begin this discussion with an overview of how we're currently treating our DME patients. There are essentially four treatment options: focal laser photocoagulation, intravitreal anti-VEGF, intravitreal corticosteroids, and surgery (which is typically reserved for a small minority of patients).[36] Dr. Eichenbaum, what's your strategy for a new, treatment-naïve patient with DME?

David A. Eichenbaum, MD, FAAO: Every new patient receives a complete dilated ophthalmic exam that includes pinhole acuity and OCT. If there's a diagnosis of moderate or severe NPDR, center-involving, visually significant DME, noncentral macular edema with ETDRS-defined clinically significant characteristics, or a suspicion of PDR, I'll also get a fluorescein angiogram (FA) on a new patient. In our referral population, most of my new patients receive an FA. If available, I prefer ultra-widefield FA and ultra-widefield fundus photographs. For 90 to 95% of patients who require treatment, my first-line recommendation is an antiangiogenic agent. If they have center-involving DME (CI-DME) and VA is worse than 20/50, I'll often start with aflibercept based on the 1-year Protocol T results.[16,19] Otherwise, I typically start with ranibizumab 0.3 mg. If a DME patient also is already scheduled for cataract surgery, or recently had cataract surgery, I may choose to treat with dexamethasone. I think the inflammatory component of cataract surgery can benefit from the corticosteroid, whereas an anti-VEGF may not treat that. Only a small percentage of my new patients are seen relatively close to cataract surgery, so only a few of my patients receive intravitreal corticosteroids first-line.

Q | Dr. Weng: Dr. Yiu, do you obtain FAs for new patients whom you suspect have DME?

Glenn Yiu, MD, PhD: It depends on the resources at hand and how busy my clinic is that particular day. I've moved away from doing traditional FA on everybody. If it's a fresh patient with new DME, I'm more likely to get an OCT and potentially an OCT-angiography (OCTA) because they take less time than FA. OCT/OCTA can also alert us if there's macular ischemia that may limit the potential visual acuity gains following anti-VEGF therapy. I get an OCT on everyone, and start with anti-VEGF therapy. I reserve FA for when there is some concern about peripheral nonperfusion or neovascularization.

Dr. Eichenbaum: Do you worry you may miss some subtle proliferative disease without the angiography and obtaining only an OCT and/or OCTA with a dilated fundoscopy?

Dr. Yiu: That's a good point. I'm often humbled by how little I can see on just clinical exam. I would prefer to obtain an FA on

more patients, but with our busy clinic I try to limit and stratify how often I request them. Someone who has mild retinopathy will probably not have an FA, whereas someone who has more moderate NPDR or who has some signs of neovascularization will have an FA.

Q | **Dr. Weng:** The logistics of obtaining an FA can be challenging, but the literature points out how much better informed we can be with advanced imaging, particularly in diagnosing patients with proliferative disease.[37-41] Dr. Bakri, when you obtain an OCT, are you looking for any imaging biomarkers that dictate your treatment selection?

Sophie J. Bakri, MD: Great question. When there's a large juxtafoveal microaneurysm, that tells me to treat with focal laser. Similarly, if there are a lot of lipids slightly away from the fovea, I might consider a grid treatment as well. We're used to treating CI-DME with anti-VEGF therapy, but I have sometimes started with a steroid first if there is a lot of DME and it looks to be inflammatory; we've had great results with that. I may begin with aflibercept for the patient who has poorer vision; I use bevacizumab or ranibizumab as a first-line treatment for patients with VA of 20/40 or better.

Dr. Weng: Let's discuss the available drugs and therapies for treating DR. There's panretinal photocoagulation (PRP), anti-VEGF therapies, and surgery for the more advanced cases of PDR. A growing 'hot topic' is the treatment of NPDR, with two clinically relevant studies (Protocol W and PANORMA) helping to guide our choices.[11,14,42-44]

Q | What do you do for a new patient who presents with a half disc area of neovascularization of the optic disc (NVD), a trace amount of vitreous hemorrhage, but who still has fairly good vision?

Dr. Bakri: Both PRP and anti-VEGF therapy are excellent options, so I'll discuss them with the patient.[11,43,44] I ask the patient to control HbA1c and other systemic factors such as hypertension. PRP can usually be done successfully in one to two sessions and is a long-term proven therapy. But some patients will still benefit from anti-VEGF therapy. There are those who want anti-VEGF treatment because 'their friend lost vision' after laser therapy—it's a myth we continue to dispel. We also need to continually stress compliance with anti-VEGF therapy, as we all have anecdotal evidence of poor outcomes that support findings in the literature when there is a gap in treatment.[45,46]

Dr. Yiu: I'm a big proponent of PRP. Data from Protocol W, Protocol S, CLARITY, and PANORAMA make a case to shift us to anti-VEGF therapy.[14,15,42,43,47,48] Relying solely on anti-VEGF is still risky. Patients in real-world settings don't have as regimented a follow-up as those in clinical trials. I like PRP, particularly for patients with PDR. Protocol S showed some visual field differences at 2 years favoring ranibizumab over PRP, although by year 5 that difference was no longer statistically significant.[15,49]

Dr. Eichenbaum: It's difficult to find patients with true ETDRS levels 47 to 53 NPDR. When I meet that patient, I need to ensure they will return because lost-to-follow-up (LTFU) is much more likely to result in a decline than whether or not I initiate anti-VEGF therapy immediately. I often don't initiate treatment at the first or second visit for these patients. Education is the biggest missing link in the diabetic patient journey. At the first visit, it's difficult to explain the risks these patients face when they have good vision and are asymptomatic. In select patients, I'll start antiangiogenic therapy sooner for severe NPDR, but when I do recommend anti-VEGF for NPDR, it's usually after I have some time and rapport with the patient.

SELECTING THE OPTIMAL ANTI-VEGF TREATMENT SCHEDULE

Dr. Weng: The vast majority of retinal specialists use anti-VEGF agents as first-line therapy for DME, and 55% of American Society of Retina Specialists members in the United States use anti-VEGF alone or in combination with PRP for high-risk PDR patients.[50] We know the best outcomes in DME are associated with frequent injections. For instance, in RISE and RIDE, patients with DME were randomized either into monthly intravitreal ranibizumab or sham injections.[6,13,51] At month 24, 18% of sham patients gained at least 15 letters versus 40 to 45% of ranibizumab patients. In VIVID and VISTA, patients with DME were randomized to aflibercept every 4 weeks (q4) or aflibercept every 8 weeks (q8) following five monthly doses or laser photocoagulation.[17,52-54] Mean BCVA gain from baseline to week 100 was greater than 11 letters in the aflibercept group versus less than 1 letter in the laser group.

Q | With these impressive gains, why aren't more of us following monthly or fixed-interval treatment approaches?

Dr. Yiu: We need to better educate patients in the real world. Many patients can do well without needing monthly treatment. Anecdotally, that's probably why so many of us use an as-needed (prn) or treat-and-extend (TAE) protocol. Diabetic eye disease is a manifestation of the systemic disorder; the severity varies with the level of control of their glycemic index. Therefore, I do a mixture of TAE and prn.

Dr. Bakri: Initially when someone comes in with DME, I use a fixed monthly approach to try to get the edema to zero and then I use a TAE regimen. Later on, I try prn if the HbA1c is better and under control, or if there hasn't been edema for a while.

Dr. Weng: Does anyone try to get DME patients completely dry?

Dr. Eichenbaum: My take has changed. There are two different kinds of patients with fluid, in my mind. The first is the asymptomatic patient with good VA, ie, 20/25. That patient can do well without treatment and can tolerate some fluid, as we found in DRCR.net Protocol V. But patients who have center-involving, visually significant DME, 20/40 or worse VA, and 325 µm of thickness on whom we initiate treatment probably need to be as

dry as possible. They also need to avoid significant and frequent fluctuations in macular thickness. If they're not dry enough or stable enough with an antiangiogenic therapy, I will use steroids.

Dr. Bakri: I don't mind watching per Protocol V, especially if they have good vision.[55] Once I decide to treat, I just can't imagine leaving some fluid and then extending the treatment interval.

Dr. Weng: I also aim to get these patients as dry as possible. I can't help but feel I'm leaving visual potential on the table when I see intraretinal fluid (IRF) sitting there for months or even years. A prn treatment approach has been mentioned by the group several times. In the purest of definitions, we would bring a patient in monthly and obtain an OCT to determine whether to treat. How do you define prn?

Dr. Yiu: I do not follow a prn scheule in that classic definition. We usually treat everybody to dry, and we start them off right away trying to reduce the edema as much as possible. It varies depending on the baseline severity of the DME. In a patient with 20/32 VA, a small amount of edema, and a very good response to treatment, I'm more likely to discontinue or to extend earlier. In patients with massive edema, I do a combination with steroid and anti-VEGF in order to reduce the edema, so I'm much less likely to choose prn and probably more likely to extend slowly. Most of those patients can't extend far beyond monthly anyway. For prn, I often will slowly extend intervals beyond 1 month. The speed at which I extend their intervals depends on how long they were stable on treatment, but I often augment with ancillary data. If their HbA1c is 10%, I'm much more likely to see them more frequently.

Dr. Weng: The fact that you consider those factors emphasizes how complex the decision-making for treatment of diseases like this really can be. Dr. Eichenbaum, do you use anatomy, vision, or both to guide your treatment decision?

Dr. Eichenbaum: I use anatomy. I like it to be constant and optimized over time. I don't think it is reasonable to expect a completely dry OCT at every visit. But you should strive for dryness, or near dryness, about 90% of the time, and certainly avoid large fluid fluctuations.

Dr. Weng: There are data to support that a prn approach can be effective. In the RIDE and RISE extension study, patients were treated following a prn schedule after the third year, and most maintained visual gains between months 36 and 48, with 25% not requiring any further injections.[54,56] In the VISTA extension study (ENDURANCE), patients were followed for an additional year after the third year of the core study; overall, the BCVA outcomes were stable, fluctuating by less than 1.5 mean letters, and 30% required no further injections.[52,57] Similarly, Protocol I showed that ranibizumab given by the protocol-specified prn treatment regimen was highly effective, with vision improving 8 to 9 letters in the ranibizumab-treated group compared to only 3 letters in the laser-treated group at 1 year.[7,58,59] During years 4 and 5, patients received a median of one or fewer injections. Protocol T compared bevacizumab, ranibizumab, and aflibercept head-to-head using a modified vision/OCT-based prn protocol.[16,60] At year 1, there was a BCVA improvement of 10 to 13 letters with all three drugs. In terms of anti-VEGF for PDR, Protocol S showed continued disease control in most patients up to 5 years with prn ranibizumab.[61] For NPDR in PANORAMA, the aflibercept q8 group was transitioned to a prn regimen in the second year.[43] Almost half still had at least a 2-step improvement in the DRSS score, but it was a smaller proportion than when they were getting q8 injections.

"I do not follow a prn scheule in that classic definition. We usually treat everybody to dry, and we start them off right away trying to reduce the edema as much as possible."

—Glenn Yiu, MD, PhD

Q | Most retina specialists use a TAE approach to manage DME. When you use a TAE regimen, do you give loading injections? Are you extending by 1 or 2 weeks? And are your decisions to extend based on OCT or VA?

Dr. Bakri: I give loading injections. When I extend, it's by 2 weeks at a time. They have to be dry before I extend, based on OCT. If they're not, I'll switch to another agent. Only visual acuity as a measure can be unreliable in clinic—patients may be tested in a different room with different lighting conditions, or they bring a different pair of glasses. Clinical visual acuity is not the same as the ETDRS readings in a clinical study. Sometimes we reach a point when we can just observe.

Dr. Eichenbaum: Dr. Bakri is correct. There's a lot of individualization that goes into patient care. If we go back to RISE and RIDE extension studies, 25% of patients did not require treatment for a long time following completion of their frequent, protocol-driven ranibizumab injections.[54,56] A minority of patients can take a long break from treatment.

Dr. Weng: What are the benefits of a nonfixed interval versus a fixed monthly approach?

Dr. Yiu: In terms of practicality, it's the patient's ability to schedule appointments. Having that flexibility is important, particularly if some patients who don't need to be seen every month can be seen less frequently.

"We must remember that in real-world studies, visual acuity is often not best-corrected and it's not standardized, so acuity measurements are different."

—Sophie J. Bakri, MD

UNDERSTANDING REAL-WORLD STUDIES

Dr. Weng: Letter gains in the real world do not align with what we observe in clinical trials. In LUMINOUS, patients received ~4.5 injections in year 1 and only gained 3.5 letters.[62] Ciulla et al used the Vestrum database to evaluate more than 15,000 patients with DME who, on average, gained 4 to 5.5 letters after about 7.5 injections during the course of the first year.[63] Visual acuity gains are consistently correlated to the number of injections, which may explain the disparity in visual acuity gains between real-world studies and clinical trials.

Dr. Bakri: We must remember that in real-world studies, visual acuity is often not best-corrected and it's not standardized, so acuity measurements are different. Secondly, compliance is a real issue; many patients don't come back every month. Patients on clinical trials are carefully selected, part of which includes their ability to come back. Other factors, such as general health, hospital visits, inability of caregivers to bring the patient to the physician, all impact follow-up.

Dr. Weng: The Wills Eye group found a LTFU (no visit for at least 1 year after an anti-VEGF injection) rate of 21.3% in white patients, 29.1% in black patients, 30.6% in Asian patients, and 35.0% in Hispanic patients ($P < .001$).[64] DME patients are uniquely challenged when it comes to compliance. They oftentimes have other medical issues that require them to prioritize other physician visits.

THE QUEST FOR INCREASED DURABILITY

Dr. Weng: Several agents with longer durability are in the pipeline and may help us reduce treatment burden for our patients. Faricimab is a bispecific molecule enveloped through a proprietary technology called CrossMAb that blocks both VEGF-A and angiopoietin-2 (Ang-2) and may allow us to treat as infrequently as every 16 weeks.

Q | What do we know from the top-line results from YOSEMITE and RHINE?

Dr. Eichenbaum: There is robust evidence confirming Ang-2 as a factor in vascular destabilization and leakage similar to VEGF.[65-69] YOSEMITE and RHINE were randomized, double masked, actively controlled trials that compared faricimab to aflibercept.[70] There were two faricimab arms, a fixed-dosing q8 week arm after loading and a personalized treatment interval (PTI). The PTI arm acted as a protocol-driven TAE; both arms were compared to aflibercept q8 weeks. Faricimab in either fixed-interval or PTI was noninferior to aflibercept with regard to visual acuity, with all groups gaining between 10 and 12 letters. In the faricimab PTI group, more than half the patients enjoyed q16 week dosing at the primary endpoint, and more than 70% were dosed every 12 weeks (q12) or longer. That's a remarkable reduction in dosing from what we currently have seen in our phase 3 trials. There was a suggestion of anatomical superiority with statistical significance favoring faricimab at some dose-matched time points, implying a potential beneficial effect to the bispecific inhibition of Ang-2 along with VEGF. Other positive results for faricimab included a greater proportion of faricimab patients at most timepoints showing an absence of DME (defined as central subfield thickness <325 µm). At a variety of time points, more patients in the faricimab arms achieved a complete absence of IRF. There was a small incidence of intraocular inflammation across all treatment groups, with inflammatory events in aggregate no more than 1% apart between the faricimab patients and the aflibercept patients, and no reported incidents of vasculitis or occlusive retinitis in any patients.

Q | **Dr. Weng:** Do you think this will become a first-line agent in the treatment of DME?

Dr. Yiu: I'm very excited about the early data. The concept of less frequent dosing is compelling. Whether or not it becomes a first-line agent will depend on real-world data and how our payors will place it. I will try to switch patients to faricimab if they are having trouble extending on other treatments.

Dr. Weng: Brolucizumab is a small single-chain antibody fragment already approved for neovascular age-related macular degeneration (AMD), but is under investigation for PDR and DME. What do we know at this point, Dr. Bakri?

Dr. Bakri: Brolucizumab has a much smaller molecular weight (26 kDa) than the other anti-VEGFs (ranibizumab is 48 kDa and bevacizumab is 149 kDa), but the clinical dose is much higher at 6 mg (compared to 0.5 mg for ranibizumab, 2 mg for aflibercept, and 1.25 mg for bevacizumab). The molar dose is also higher with brolucizumab (between 11 and 13, compared to ranibizumab at 0.5 to 0.6, aflibercept at 1, and bevacizumab at 0.5). KESTREL and KITE are 2-year, phase 3 multicenter studies.[71,72] The 52-week data was presented at ARVO. Patients were randomized to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg in KESTREL and only brolucizumab 6 mg or aflibercept 2 mg in KITE. In both studies, brolucizumab met the primary endpoint of noninferiority to aflibercept at week 52. Brolucizumab also showed a significantly greater improvement as compared to aflibercept in central subfoveal thickness; patients in the brolucizumab arms were also

drier. Intraocular inflammation rates in KESTREL were 4.7% for brolucizumab 3 mg (including 1.6% retinal vasculitis), 3.7% for brolucizumab 6 mg (including 0.5% retinal vasculitis), and 0.5% for aflibercept 2 mg. Idiopathic orbital inflammation rates in KITE were equivalent (1.7%) between the brolucizumab 6 mg and aflibercept 2 mg arms with no retinal vasculitis reported. Retinal vascular occlusion was reported in KESTREL for brolucizumab 3 mg (1.1%) and 6 mg (0.5%), and in KITE for brolucizumab and aflibercept (0.6% each). The majority of these events were manageable and resolved with or without treatment.

Dr. Yiu: Some of the intraocular inflammation (IOI) from the brolucizumab trials struck me as rather different from the IOI seen with other anti-VEGF agents in the past. Unlike mild anterior chamber or vitreous cell that has been attributed to manufacturing impurities for other products, which has been largely ruled out with brolucizumab, the occlusive vasculitis seen with brolucizumab is very different in nature. You almost have to wonder whether it's a physiological effect from essentially injecting a 20x ranibizumab dose. Right now, we just don't know how to easily identify those patients.

Dr. Eichenbaum: That very well might be why—the extremely high molarity brolucizumab injection may be why we're seeing some IOI. It might not have anything to do with purification or manufacturing. The jury is still out on the etiology of the IOI we have seen with brolucizumab.

Dr. Yiu: While we are all very familiar with aflibercept, the PHOTON phase 2/3 study (NCT04439503) is evaluating a high-dose 8 mg aflibercept versus the standard 2-mg dose for treatment of patients with DME. This study comes on the heels of a successful phase 2 study in wet AMD patients (NCT04423718) where 8 mg aflibercept given at q12 week dosing after three monthly loading doses showed a higher proportion of patients staying dry compared with 2 mg aflibercept. Because aflibercept is a familiar product for most providers and many patients have had excellent control already on this drug, the concept of a higher dose to allow greater durability or extension intervals is quite appealing.

Q | Dr. Weng: Two gene therapies have potential to treat diabetic eye disease: ADVM-022 and RGX-314. Dr. Yiu, can you give us a brief overview?

Dr. Yiu: ADVM-022 is a viral vector that essentially makes aflibercept,[73] and RGX is a viral vector that essentially makes ranibizumab.[74] Their delivery methods differ. Adverum uses a novel AAv.7m8 serotype. Traditionally, AAV vectors had to be injected subretinally because that's the only way to get the virus into the photoreceptors. AAV injected into the vitreous cavity is otherwise blocked from entering the retina due to the internal limiting membrane barrier. However, through a process known as directed evolution, this newer generation AAV.7m8 capsid has been developed that allows this virus to penetrate into the retina when injected into the vitreous cavity.

The INFINITY DME studies (NCT04418427) looked at two doses of the treatment—a low-dose 2x 10^11 vg/eye and high-dose 6 x 10^11 vg/eye—and compared it to aflibercept. That study was halted early when a patient suffered uveitis and hypotony that could not be rescued; so the entire cohort has been unmasked to further investigate the risk of inflammation.[75] It is still very unclear what happened. The subretinal space is more immune privileged than the vitreous cavity, so the viral vector may be exiting the eye. It's well known that intravitreally injected compounds can leak into systemic circulation and trigger an immune response. We don't know. All we know is that a patient in the high-dose cohort suffered panuveitis, hypotony, and vision loss at 30 weeks after the one-time treatment. The fact that this adverse response was so long after the initial dosing is also concerning because that indicates to me it may be unpredictable. Of note, the same viral vector is being investigated in AMD without the same safety issues (NCT03748784 and NCT04645212), suggesting the underlying disease may have a significant role in determining who may develop inflammation after this gene therapy.[73]

RGX-314 is an AAV8 vector delivered via the suprachoroidal space that is being evaluated for DR—not DME—in the ALTITUDE study (NCT04567550).[74] RGX-314 was originally developed to be delivered subretinally, but subretinal injections are limited to a small bleb where the effect occurs. It's also a more complex process that requires vitreoretinal surgery. Using a microneedle to deliver a viral vector to the suprachoroidal space is very attractive and potentially more effective for a disease like DR. ALTITUDE is a phase 2 study comparing RGX-314 at 2 x 10^11 GC/eye and 5 x 10^11 GC/eye. The primary endpoint of the trial is the proportion of patients with DR severity improvements based on the ETDRS-DRSS at 48 weeks. Other endpoints include safety and development of DR-related ocular complications.

What's interesting is this study does not use prophylactic steroids because the sponsor feels the delivery location of the viral vector should trigger minimal IOI. It will be interesting to see how long these viral vectors last and if there are complications with long-term VEGF suppression that you can't turn off.

Q | Dr. Weng: Dr. Yiu, observation has taught us that subretinal injections are generally better tolerated than intravitreal ones in terms of IOI. Suprachoroidal delivery is still in its infancy. What are your thoughts on the immunogenicity of suprachoroidal injections?

Dr. Yiu: Numerous studies have proven the efficacy of delivering steroids into the suprachoroidal space.[76-87] But we don't know about that same efficacy with a viral vector because some of the research studies including those from my lab used nonhuman primates and we were delivering green fluorescent protein, which is a protein derived from jellyfish. Obviously, we would expect the body to generate some immunity to this foreign protein. However, if you are making a human or humanized protein, like many of the products under investigation, the risk of the immunogenicity could

be lower. But the fact is we don't know if the immune responses to gene therapy are caused by the viral vector, the promoter, the therapeutic gene, or even the underlying disease. In the INFINITY trial, patients who developed inflammation were primarily patients with diabetes, who often are considered to have some degree of immune compromise.

Dr. Weng: While most of the agents we have discussed target VEGF-A, OPT-302 is a drug candidate that blocks VEGF-C and VEGF-D. Tell us about this, Dr. Eichenbaum.

Dr. Eichenbaum: Another novel approach is to inhibit additional isoforms of VEGF. Currently, all VEGF inhibitors block VEGF-A. There are multiple other members of the VEGF cytokine family, including VEGF-B, VEGF-C, VEGF-D, and VEGF-E. These bind to additional VEGF receptors, and it is possible that inhibiting more of the VEGF pathway will lead to superior anatomic and visual results. OPT-302 is a novel VEGF-C/-D inhibitor and was shown to improve the outcome when combined with anti-VEGF therapy.[88] Remarkably, in a randomized phase 2 trial (NCT00397264), OPT-302 in combination with aflibercept showed superiority in both anatomy and vision compared to ongoing aflibercept monotherapy in patients incompletely responsive to previous treatment with aflibercept monotherapy. An OPT-302 phase 3 program in DME patients is pending; there is an ongoing phase 3 program in wet AMD (COAST; NCT04757636).

Dr. Weng: Dr. Eichenbaum, what do we know about KSI-301?

Dr. Eichenbaum: KSI-301 is a novel antibody biopolymer conjugate that inhibits VEGF with potentially more stability, durability, and tissue bioavailability than current anti-VEGF therapies. The phase 1b, single-ascending, dose-escalation (1.25 mg, 2.5 mg, and 5 mg) study found that KSI-301 was well-tolerated at all dose levels (NCT03790852). Rapid improvements in BCVA and anatomy were seen as early as week 1 after treatment. There were no drug-related adverse events, inflammation, or dose-limiting toxicities. There was also sustained BCVA improvement of 9 letters at 12 weeks across all dose levels. The phase 1b trial is ongoing, and this data set has been updated, examined, and presented during the past 2 years with continued follow-up.[89]

We do have several phase 2 and phase 3 trials enrolling in wet AMD, DME, and NPDR (DAZZLE, NCT04049266; GLEAM, NCT04611152; GLIMMER, NCT0460393; and GLOW, NCT05066230).[88] DAZZLE, GLEAM, and GLIMMER are comparing KSI-301 with dosing up to 24 weeks with aflibercept on label. What we're going to look for in DME, of course, is how many of those KSI-301 patients have a stable retina out to these long-interval timepoints. GLOW is still enrolling, and it will evaluate the safety and efficacy of KSI-301 in NPDR patients versus sham. Although KSI-301 has promising durability based on the available data, we don't have a lot to go on other than the open-label phase 1b dataset, so we're going to have to wait and see results from these controlled series. In DME, we could see durability to rival or surpass the phase 3 results we've seen for faricimab in YOSEMITE and RHINE.

It's going to be interesting to see if we can do one or two injections a year and have a meaningful regression in DR similarly to what we see in PANORAMA with three or four injections a year. The risk with KSI-301 is that its pharmacokinetics may be different; it may not penetrate into the retina quite like aflibercept or ranibizumab. KSI-301 is a large bolus. The design is such that it sheds an aflibercept-like substance with a presumably small size, and we have to see how it compares to aflibercept itself with a relatively low molecular weight. These trials will reveal if KSI-301's aflibercept-like substance behaves like liquid aflibercept.

Dr. Weng: Dr. Bakri, tell us about the PDS. This is a surgical option that could allow treatment as infrequently as every 6 months, maybe even longer.

Dr. Bakri: PDS is a permanent refillable ocular implant that's surgically placed at the pars plana. The refill injection, which is given in the office, includes a special formulation of ranibizumab. PDS is under investigation in DME and DR without DME in the PAGODA (NCT04108156) and PAVILION (NCT04503551) trials, respectively.

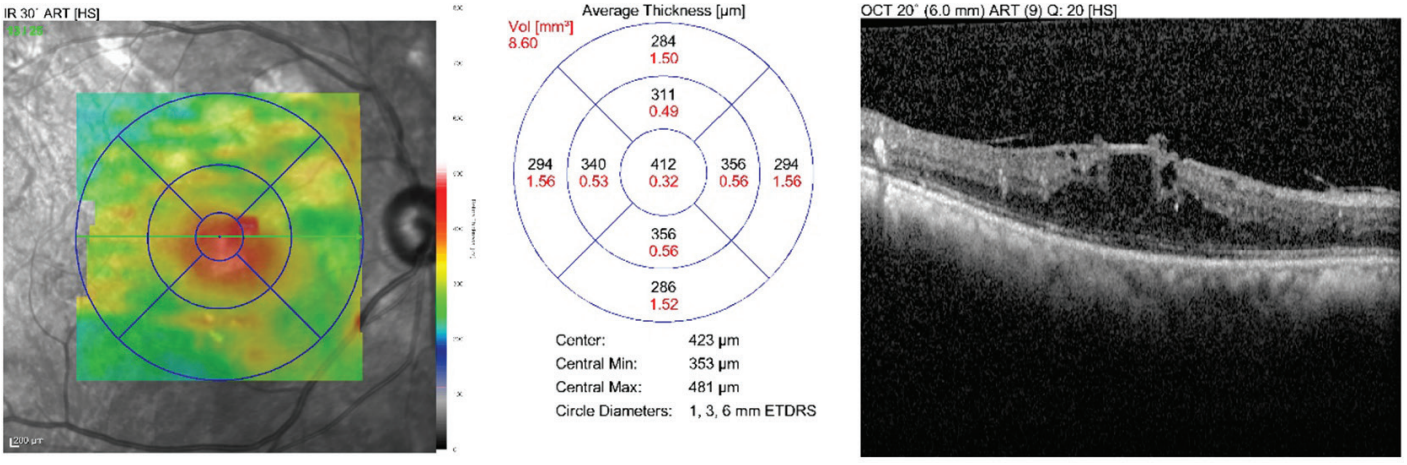

Figure 1. Case 1: Baseline imaging.

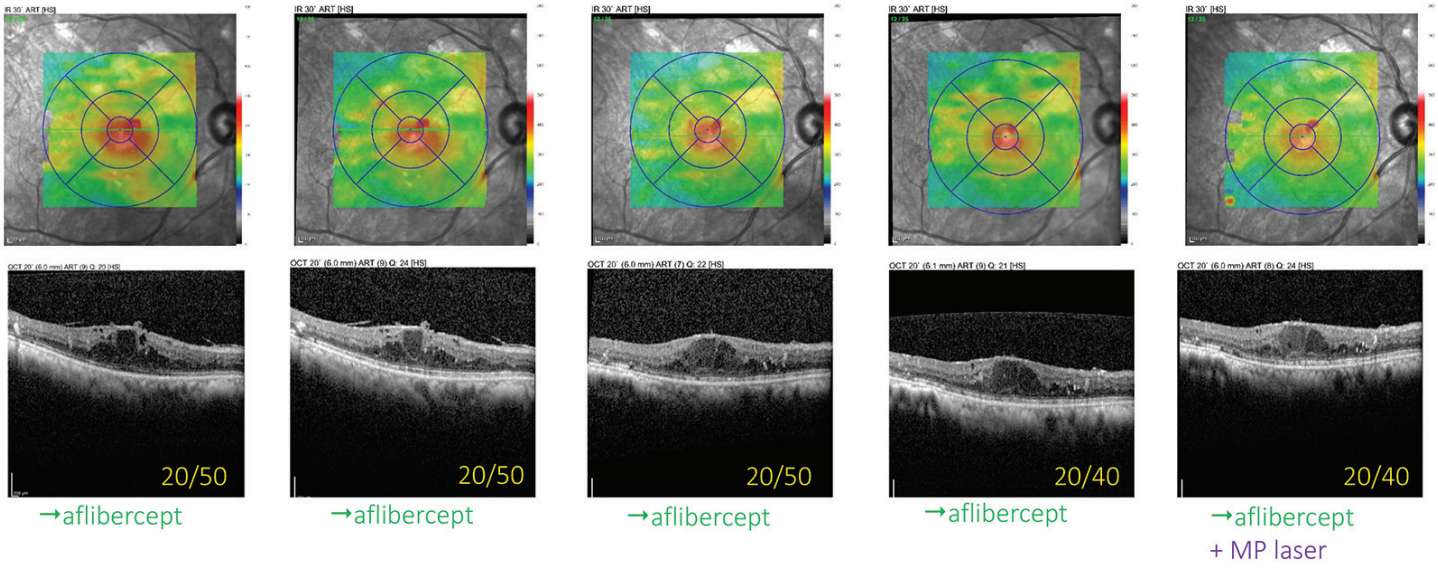

Figure 2. Case 1: Imaging after monthly aflibercept.

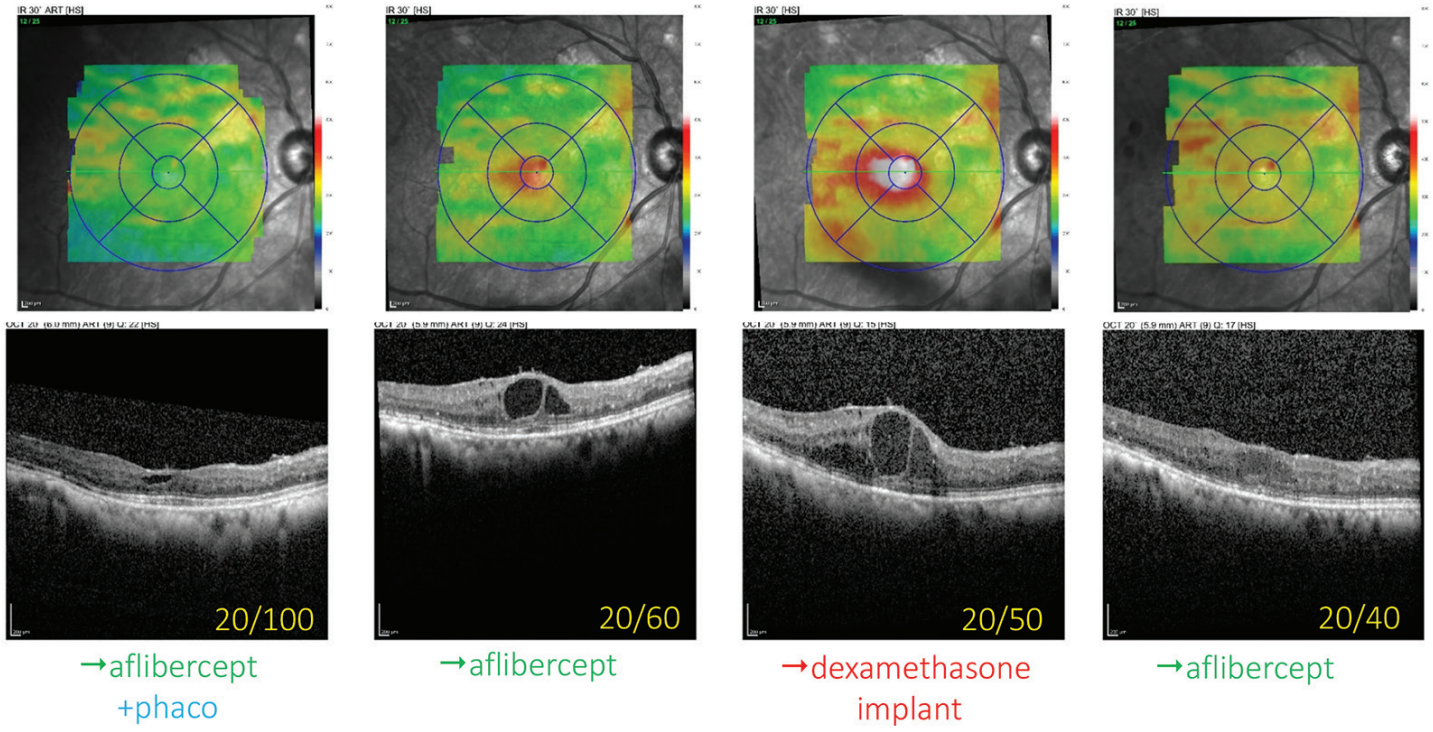

Figure 3. Case 1: Imaging after dexamethasone implant.

PDS will be compared to ranibizumab in terms of best visual acuity and central subfield thickness. We are currently awaiting data.

Editor's note: The FDA approval of the ranibizumab injection 100 mg/mL for intravitreal use via ocular implant for wet AMD, previously called the port delivery system (PDS), occurred after the recording of this virtual roundtable.

CASE 1: CENTER-INVOLVING DME

Dr. Yiu: Our first case is a 66-year-old physician with a history of DME. She had focal laser 4 years ago. She came to me with center-involving DME with a little bit of an epiretinal membrane (Figure 1). I started her on monthly aflibercept. Her VA improved very slightly from 20/50 to 20/40 (Figure 2), but she had persistent edema. At what point do you consider switching agents or adding a steroid?

Dr. Bakri: Aflibercept is generally a safe treatment. If the patient had IOI after aflibercept, I would switch to ranibizumab. Another situation in which I would switch to ranibizumab would be if the patient initially was responding well to ranibizumab, stopped responding and was switched to aflibercept, then became refractory. These are rare cases, but I have seen patients become used

to a treatment and then it stops working. In this case, I would give the patient several monthly aflibercept injections before moving on to another treatment, and my next line treatment in this case would be intraocular steroid therapy.

Dr. Eichenbaum: I've done it in a different situation. If a patient has a stroke and doesn't come in for 2 to 3 months, I'll start them on ranibizumab if they have recurrent disease. There's some evidence that ranibizumab is a little safer in stroke patients.[90]

Dr. Weng: To me, there's a difference in patients who are non-responders versus those who are slowly getting thinner. For the latter group, I will continue monthly anti-VEGF. But in patients who continue to have fluid, I'm quick to integrate steroid therapy.

Dr. Yiu: I also like to introduce steroids much earlier, especially when anti-VEGF therapy has barely touched the fluid. It's different if you see some improvement initially, so the patient may just need more time. In this case, however, the edema seemed refractory to anti-VEGF treatment, and I would have started her on steroids much earlier. The issue is that she was phakic and refused steroids due to some research she did on her own. I kept injecting her with aflibercept and even tried micropulse laser. At one point I convinced her to try subtenon steroids, but there was not much improvement either. Over time, the edema slowly improved, but her visual acuity worsened, and she developed a cataract. She eventually underwent cataract surgery, and she developed more edema. At this point, I suspected this was a combination of pseudophakic cystoid macular edema and/or worsening of the DME. We finally gave her a dexamethasone implant, and her VA improved to 20/40 (Figure 3).

Dr. Eichenbaum: This case teaches me that I should use steroids sooner.

Dr. Yiu: I agree. I am more persistent with anti-VEGF monotherapy in patients who show some response. But if they are unresponsive like this case, I'm more likely to recommend steroids earlier.

CASE 2: BILATERAL NVE, DELAYED TREATMENT

Dr. Bakri: Our second case is a 76-year-old white male, 20/20 VA OD and 20/25 OS. He's pseudophakic and has mild epiretinal membrane in both eyes. He has early PDR without DME. He has type 2 diabetes with vascular complications including amputation. His last HbA1c 3 months prior was 8.5% and he has nephropathy. The Optos color photograph shows dot blot hemorrhages in four quadrants (Figure 4). I can't see any NVD. The FA shows several patches of neovascularization elsewhere (NVE) in both eyes and some capillary nonperfusion in the periphery (Figure 5). There is a mild epiretinal membrane on OCT and there appears to be a posterior vitreous detachment. There's no macular edema in either eye. How would you treat this patient?

Dr. Eichenbaum: Both eyes need treatment. I use anti-VEGF as the backbone of treatment initiation in essentially all patients

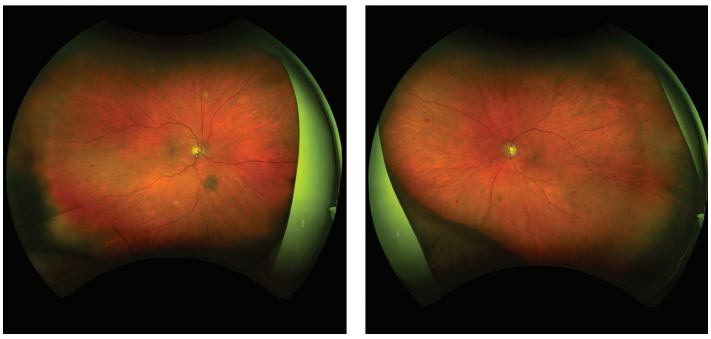

Figure 4. Case 2: Baseline Optos color photographs.

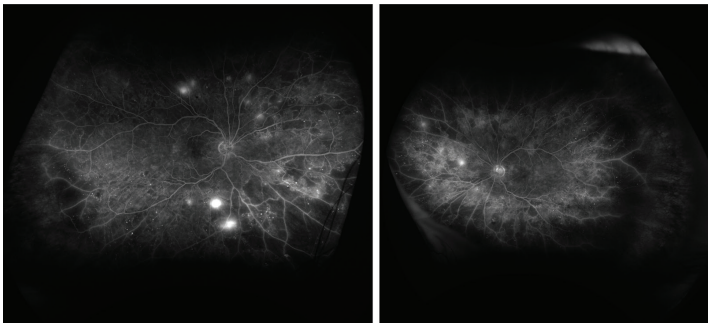

Figure 5. Case 2: Baseline angiogram.

with PDR. I start with an anti-VEGF on the day that I initiate treatment, and the patient and I have that discussion. Even if they are asymptomatic, I talk to them about PDR. Sometimes if only one eye is worse or one eye is symptomatic with a few floaters, I'll treat that one. I'll treat both eyes if the patient is willing. I alternate anti-VEGF and laser; I don't do PRP on the same day. I typically do three sessions of PRP somewhere between spot sizes of 100 to 400 µm three times, and then I consider it a full pattern. I alternate that with anti-VEGF, and then generally stop everything if there's no DME. I'll then see what happens 3 months after the last PRP treatment. It sounds like a lot of treatment, but if we stick to the plan, the patient probably won't see much of me after the first year.

Dr. Bakri: The patient received monthly intravitreal anti-VEGF injections for PDR. There was some stability and some NVE regression after several months. There was a 6-month delay in treatment, and the patient came back with a vitreous hemorrhage due to PDR. It's important to acknowledge that we read clinical trial data about the utility of anti-VEGF therapy in PDR, but it's easy to forget the LTFU that happens in the real world.

Dr. Weng: Great case, Dr. Bakri. It reminds us that real-world behavior does not mimic the behavior we see in clinical trials. Although we can't guess how patients will behave, I do try to glean an assessment of adherence and factor that into my decision-making.

As you can tell from our discussion, we have several promising agents in the pipeline that either work through a different mechanism of action or allow for a longer durability—perhaps even greater efficacy—for the treatment of diabetic eye disease. The future is very bright, and I want to thank the faculty for their engaging insights and cases. ■

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INSTRUCTIONS FOR CME CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to http://evolvemeded.com/course/2127-2supp. 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.

Full Name_____

Phone (required) _____ Email (required*) _____

Address/P.O. Box _____

City _____ State/Country____ Zip/Postal Code_____

License Number _____ OE Tracker Number _____

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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 activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

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

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

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the pros and cons of current therapy options for diabetic eye disease	_____	_____	_____
Articulate the challenges facing retina specialists related to the complexities of managing patients with diabetic retinopathy and diabetic macular edema	_____	_____	_____
Assess pipeline candidates under investigation for these patient populations	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability your confidence in your ability to implement individualized patient treatment plans to ensure optimal outcomes for patients (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. Based on this activity, please rate your confidence in your ability to identify the relationships between retinal disease characteristics, drug, treatment frequency, visual and anatomic outcomes (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

3. A new patient presents for a diabetic eye exam. He is 45-year-old male with poorly controlled type 2 diabetes (HbA1c of 11%). His VA is 20/60 OU. There is some evidence of center-involved diabetic macular edema (DME) and questionable neovascularization in the far temporal periphery. In addition to OCT, what imaging is recommended for this patient?

a. Fluorescein angiogram
b. Ultra-widefield fluorescein angiogram
c. Indocyanine green angiography
d. Fundus autofluorescence

4. You confirm the patient from question 3 has center-involved DME, intraretinal hemorrhages in all four quadrants, but no NV. What is the recommended first-line therapy for this patient?

a. Intravitreal steroids
b. Subtenon steroids
c. Anti-VEGF injections
d. Focal laser

5. According to the RISE and RIDE extension studies, what percent of patients with DME will maintain visual gains and not require further anti-VEGF injections for 2 years with as-needed therapy?

a. 25 - 30%
b. 50 - 60%
c. 40 - 45%
d. 10 - 15%

6. What are some common reasons clinical trial outcomes do not translate to the real-world setting? Select all that apply.

a. Patients in the real-world have competing appointments and multiple comorbidities and are more likely to be lost to follow-up
b. Patients are followed for longer periods in clinical trials compared to the real-world setting
c. Ethnic minorities are over-represented in clinical trials, which makes it difficult to apply clinical trial data to real-world patient populations
d. Acuity measurements in the real world are different from those in clinical trials

7. Based on top-line results from YOSEMITE and RHINE, faricimab has shown a lasting durability of up to _____.

a. 14 weeks
b. 8 weeks
c. 16 weeks
d. 12 weeks

8. The INFINITY trial of ADVM-022 (AAV.7m8-aflibercept) in patients with DME was halted because _____.

a. Some patients developed occlusive vasculitis
b. Some patients developed hypotony and uveitis
c. There was no improvement in visual acuity
d. There was no improvement seen in DME severity

9. _____ is a gene therapy currently in development for diabetic retinopathy.

a. ADVM-022
b. RGX-314
c. OPT-302
d. KSI-301

10. Which statement regarding OPT-302 is accurate?

a. OPT-302 is a molecule that blocks VEGF-A and angiopoietin-2
b. OPT-302 is a molecule that blocks VEGF-C and VEGF-D and may be used in conjunction with an anti-VEGF-A agent
c. OPT-302 is a surgically implanted device that could significantly reduce the treatment burden for patients with DME
d. OPT-302 should be used to treat primarily patients with DME and VA of at least 20/25

ACTIVITY EVALUATION

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

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

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

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

Probability of changing practice behavior based on this activity: _____ High _____ Low _____No change needed

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

Change in pharmaceutical therapy _____

Change in nonpharmaceutical therapy _____

Change in diagnostic testing _____

Choice of treatment/management approach _____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

I do not plan to implement any new changes in practice ___

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

_____ Cost

_____ Lack of consensus or professional guidelines

_____ Lack of administrative support

_____ Lack of experience

_____ Lack of time to assess/counsel patients

_____ Lack of opportunity (patients)

_____ Reimbursement/insurance issues

_____ Lack of resources (equipment)

_____ Patient compliance issues

_____ No barriers

Other. Please specify: _____

_____

_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

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

_____ Patient Care

_____ 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 ask if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____