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Diabetic Eye Disease Collaborative Care:

The Latest Treatment Innovations and Real-World Uses

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Diabetic Eye Disease Collaborative Care: The Latest Treatment Innovations and Real-World Uses

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Content Source

This continuing education (CE) activity captures content from a synchronous in-person virtual symposium.

Activity Description

This supplement summarizes a discussion on managing patients with diabetic eye disease, including real-word barriers to treatment, longer duration therapies, and pipeline therapies.

Target Audience

This certified CE activity is designed for optometrists.

Learning Objectives

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

- **Review** advances in current treatments for diabetic eye disease and nAMD
- **Identify** patients who may benefit from advances in the treatment paradigm for retinal vascular diseases
- **Formulate** strategies to identify and resolve barriers to optimal treatment outcomes for patients with nAMD and diabetic eye disease
- **Summarize** therapies for retinal vascular diseases that are in clinical development

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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 ability to formulate strategies to identify barriers to optimal treatment outcomes for patients with diabetic macular edema (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. A 55-year-old patient has a history of diabetes for 10 years. His most recent HbA1c was 8.4%, and his blood pressure was 138/78 mm Hg. He presents for a routine dilated eye exam during which moderate intraretinal microvascular abnormalities are observed in his right eye, with microaneurysms, intraretinal hemorrhages, and diabetic macular edema (DME) in his left eye. His VA is 20/20 in both eyes. What is the next best step to potentially maintain this patient's visual acuity?

a. Recommend a follow-up visit in 3 months
b. Recommend a follow-up visit in 3 months and educate the patient on the importance of a healthy diet and moderate exercise
c. Refer to a retina specialist for evaluation of potential treatment with intravitreal aflibercept 8 mg or faricimab
d. None of the above

3. Faricimab, approved for the treatment of wet age-related macular degeneration, DME, and macular edema following retinal vein occlusion, targets which of the following molecular facilitators of angiogenesis?

a. VEGF-A
b. VEGF-A and angiopoietin-2
c. VEGF-A and VEGF-B
d. VEGF-A and angiopoietin-1

4. A 66-year-old patient, who is a structural engineer, is currently receiving intravitreal aflibercept 2 mg injections for DME in both eyes. He has a history of diabetic kidney disease. His VA has improved from 20/50 to 20/25 after treatment with aflibercept 2 mg. Which of the following demographic or clinical factors is associated with the highest risk of loss to follow-up (LTFU) for this patient?

a. Diabetic kidney disease
b. Older age
c. High socioeconomic status
d. Improved visual acuity after anti-VEGF treatment

5. A 35-year-old patient presents with center-involving DME and 20/40 VA in her right eye. She states that she is a single mother and works two jobs to support her family. What is the next best step in this patient's care?

a. Schedule a 6-month follow-up visit
b. Refer the patient to a retina specialist for evaluation of potential treatment with intravitreal corticosteroid
c. Refer the patient to a retina specialist for evaluation of potential treatment with off-label intravitreal bevacizumab
d. Refer the patient to a retina specialist for evaluation of potential treatment with intravitreal faricimab

6. Which of the following statements is TRUE regarding the 52-week outcomes of patients with moderately severe to severe nonproliferative diabetic retinopathy in the Pavilion trial?

a. Port Delivery System with ranibizumab (PDS) Q36W was associated with significantly greater Diabetic Retinopathy Severity Scale (DRSS) worsening
b. PDS Q36W significantly lowered the rate of center-involving DME and vision-threatening complications
c. PDS Q36W was inferior to the control arm in a 2-step or more DRSS improvement
d. PDS Q36W significantly improved BCVA, with a trend toward improved central subfield thickness

7. Which of the following statements is TRUE regarding the key findings of the Yosemite and Rhine trials in patients with DME?

a. Faricimab had noninferior visual outcomes and comparable anatomic outcomes to aflibercept 2 mg over 2 years
b. Faricimab had better visual and anatomic outcomes compared to aflibercept 2 mg over 2 years
c. Faricimab had noninferior visual outcomes and comparable anatomic outcomes to panretinal photocoagulation over 2 years
d. Faricimab had better visual and anatomic outcomes compared to panretinal photocoagulation over 2 years

8. What percentage of patients with wet age-related macular degeneration or DME who were treated with faricimab achieved extended durability of Q12W or more dosing?

a. 20%
b. 40%
c. 60%
d. 80%

9. A 74-year-old patient with a history of diabetic eye disease for 5 years presents to your clinic. He states he has poor adherence to monthly anti-VEGF therapy because he is overwhelmed by other physician appointments with his dentist and endocrinologist. Which of the following intravitreal therapies is LEAST appropriate to treat his DME?

a. Ranibizumab
b. Faricimab
c. Aflibercept 8 mg
d. Brolucizumab

10. A 38-year-old Asian patient who is a dentist presents with proliferative diabetic retinopathy and a VA of 20/40 OU. Which of the following assessments and plans are most appropriate to manage this patient?

a. Patient is at a low risk for LTFU because of his age, race, and socioeconomic status; therefore, extended durability treatments are not necessary to consider
b. Patient is at a low risk for LTFU because of his age alone; however, extended durability treatments should always be considered
c. Patient is at a high risk for LTFU because of his age, race, and socioeconomic status; therefore, extended durability treatments should be considered
d. Patient is at a high risk for LTFU because of his age alone; therefore, extended durability treatments should be considered

11. All the following patients treated with anti-VEGF therapy for diabetic eye disease may benefit from switching to more durable anti-VEGF agents, EXCEPT?

a. A 65-year-old patient who lacks transportation
b. A 42-year-old patient with an improved VA of 20/20 after treatment
c. A 72-year-old patient with an improved VA of 20/30 after treatment
d. An 82-year-old patient with a left below-the-knee leg amputation

Diabetic Eye Disease Collaborative Care: The Latest Treatment Innovations and Real-World Uses

Barriers to Care in Diabetic Eye Disease

ROGER A. GOLDBERG, MD, MBA

Diabetic eye disease comprises diabetic macular edema (DME) and diabetic retinopathy (DR); DR can be subtyped to proliferative DR (PDR) or nonproliferative DR (NPDR). A 2021 estimate of DR prevalence revealed that DR rates are much higher than previously estimated: approximately 26% (9.6 million) of Americans with diabetes have DR, and 5% (approximately 1.8 million) of patients with diabetes have vision-threatening DR.[1] Approximately 746,000 Americans have DME.[2]

A clear connection exists between long-term HbA1c levels and risks of diabetes-related complications. The Diabetes Control and Complications Trial showed that lower hemoglobin A1c levels correlated with lower risks of diabetes-related complications.[3] A 1% decrease in HbA1c levels can reduce the risk of progression by up to 50% for second-order effects such as retinopathy, nephropathy, and neuropathy.[4] Patients in the UK Prospective Diabetes Study who were observed over a 10-year period were 25% less likely to require photocoagulation for DR if the mean HbA1c levels were 7.0% compared with 7.9%.[5]

Risk factors for DR include duration of diabetes, poor control of diabetes, high blood pressure, coexistent nephropathy or kidney disease, obesity, hyperlipidemia, smoking, and pregnancy.[6-10] Of course, smoking cessation and control of blood sugar, blood pressure, and cholesterol are key to successful management of diabetes. Medical management using those key tactics should always be recommended to patients with diabetes.

Optometrists and ophthalmologists play an important role in educating patients about the importance of medical management of diabetes, and successful efforts may yield fewer instances of vision-threatening disease for patients. As primary eye care providers, optometrists have a unique opportunity to discuss medical management of diabetes with patients in its earliest stages; indeed, many retina specialists don't encounter patients with diabetes until their visual disruption has reached the point that it requires therapy, at which point A1c control has typically been poor for some period of time. In contrast, optometrists often see patients for routine care before disease manifestations adversely affect vision. For patients, reiterated instruction on medical management of diabetes is important, and when all providers (eg, primary care providers, endocrinologists, etc.) are on the same page, the patient receives a single, clear message.

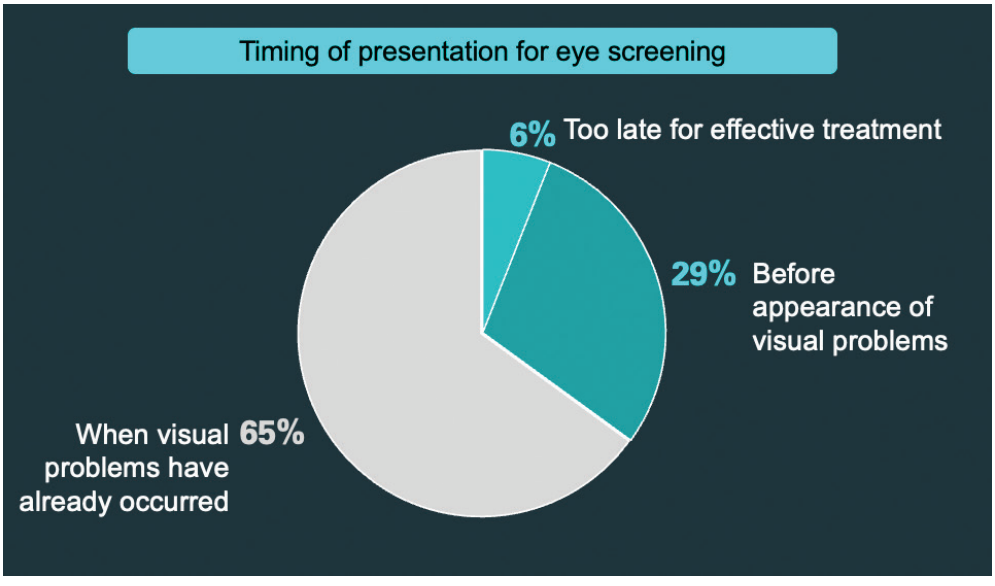

Figure 1. Nearly two-thirds of patients with DR are screened for disease when they present to an eye care provider after experiencing visual decline, per the DR Barometer Study. Only 29% of patients present before the onset of visual disruption. If more patients experienced earlier DR diagnosis due to enhanced screening protocols, then the risk of ocular complications and visual compromise may be reduced. Adapted from: Cavan D, Makaroff L, da Rocha Fernandes J, et al. *Diabetes Res Clin Pract.* 2017;129:16-24.

SCREENING CHALLENGES

Early detection of DR is key to thorough monitoring and treatment, but challenges to disease detection persist. The DR Barometer Study, which was a survey comprised of 4,340 patients with diabetes in 41 countries, found

TABLE. DR SCREENING RECOMMENDATIONS

	Recommended Initial Evaluation	Recommended Follow-up
T1DM	5 years after diagnosis	Annually
T2DM	At time of diagnosis	Annually

Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

that 65% of patients with DR present when visual disruption is already present.[11] Intuitively, this makes sense: many patients make an appointment with an eye care provider when they notice visual changes. The same study also found that 6% of patients with DR present after disease has advanced so far that treatment is ineffective, and that 29% of patients present before the manifestation of visual disruption (Figure 1).

Closer adherence to screening guidelines may be an effective means by which to detect DR in patients before it affects vision. The most recent American Academy of Ophthalmology DR Preferred Practice Pattern Guidelines suggests different screening practices for patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).[12] Patients with T1DM, sometimes called early-onset diabetes or juvenile diabetes, should be screened for DR 5 years after diagnosis, and annually thereafter. Patients with T2DM should be screened promptly at diagnosis of T2DM, with follow-up each year (Table). It is advised that patients with T2DM are screened promptly because it is assumed that they have been living with T2DM for an undetermined period prior to diagnosis.

We must stress to patients that follow-up is needed even if they are not experiencing visual symptoms: we cannot detect disease early if they don't present as suggested. In 2016, Ziemer et al found that patients with diabetes who are already in the care of a provider are most likely to be screened for DR—but also found that 71% of patients with diabetes do not receive DR screening.[13] Further, 50% of patients do not follow up with eye care providers as recommended.

TREATMENT CHALLENGES

Even after patients are diagnosed with DR or DME, they still face significant hurdles to compliant treatment. Retina specialists administering anti-VEGF injections to treat these diseases recognize that monthly injections—despite being the standard dosing regimen described in the earliest entries into the literature[14,15]—are too burdensome on patients. Among real-world patients, as illustrated by Ciulla et al, the number of injections in the first year correlates in a near-linear fashion with better vision outcomes (Figure 2).[16]

In an effort to alleviate the burden associated with monthly injections, retina specialists have evaluated quarterly,[17] prn (ie, as-needed),[18] and treat-and-extend (TAE) regimens.[19] In the United States, 57% of retina specialists employ TAE regimens,[20]

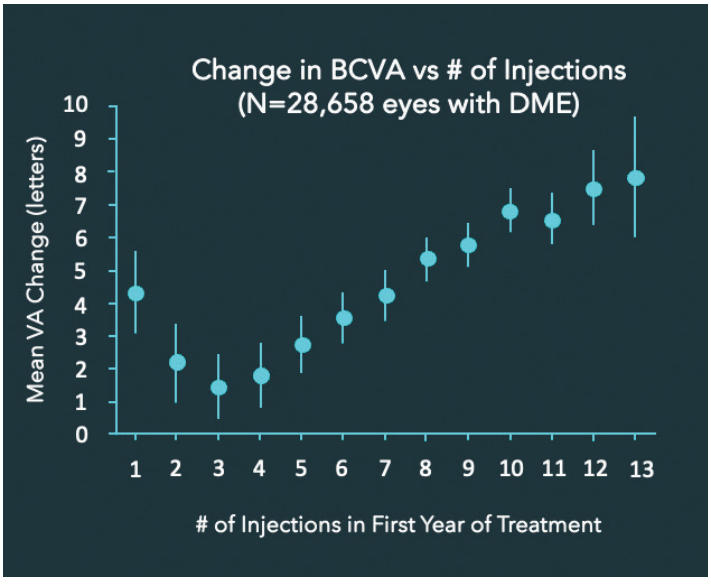

Figure 2. During the first year of treatment for DME, the number of anti-VEGF injections correlates with mean change in visual acuity from baseline. Still, frequent anti-VEGF injections are burdensome, and patients face various barriers to receiving consistent monthly therapy. Reproduced from Ciulla TA et al. *Br J Ophthalmol.* 2021;105:216-221; with permission from BMJ Publishing Group Ltd.

and in real-world settings evaluating TAE regimens for DME, it has been shown to be noninferior to monthly dosing.[21]

Debating the merits of various dosing regimens is beyond the scope of this discussion. Rather, we should see the number of arrows in a retina specialist's quiver as a sign that DR is a heterogenous disease that responds variously according to any number of factors.

One of those factors, of course, is patient compliance to dosing recommendations. It is difficult to pin down any single factor linked to patient noncompliance, but Baumal et al identified several factors as existing within the matrix of nonadherence to therapy. They can broadly be grouped as socioeconomic (eg, high out-of-pocket costs for care, lack of education), practical (eg, lack of transportation, vacation), psychologic, (eg, fear of injections, fear of poor prognosis, depression/anxiety), and medical (eg, other illnesses that take priority, lost mobility).[22]

Despite the scientific advances that the first generation of anti-VEGF therapies represent, these innovations are useless if the barriers to care prevent patients from visiting the clinic. The advent of treatments that allow longer durations between visits could significantly mitigate the barriers outlined above without sacrificing the quality of care delivered to the patient. Prompt referral from an optometrist to a retina specialist will be key getting patients in the chair, but referral alone is insufficient: optometrists must arm their patients with urgency and education to ensure that they receive the highest level of care with the greatest likelihood of efficacy.

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WHAT IS ANGIOPOIETIN-2, AND WHAT DOES IT HAVE TO DO WITH DME?

Historically, eye care providers focused on VEGF inhibition, as the only therapies available for treatment of retinal vascular diseases were anti-VEGF agents. However, other biologic factors are at play in diseases such as diabetic macular edema (DME). One of the biologic components we are beginning to better understand is angiopoietin.

In healthy eyes, a balance of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) maintains vascular stability.[1] However, when Ang-2 is upregulated and the Ang-1/Ang-2 balance is disrupted, two events occur: increased neovascularization and vascular instability, and the sensitization of blood vessels to the effects of VEGF-A.[2] Because patients with DME have increased vitreal concentrations of Ang-2,[3] inhibition of Ang-2 may be beneficial in some patients.

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Longer Duration Therapies as a Potential Solution for Diabetic Eye Disease

A. PAUL CHOUS, MA, OD, FAAO

In the 2023 American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) survey, 43% of US retina specialists said that administrative and insurance burdens were the leading socioeconomic challenge for treating patients with diabetic macular edema (DME).[1] The second-leading challenge (35%) to treating patients was frequent loss to follow-up (LTFU).

Research on the matter backs up retina specialists' response. Approximately 25% of patients with nonproliferative diabetic retinopathy (NPDR) and DME did not return for a follow-up visit following a single injection of anti-VEGF in a 2019 study.[2]

Among patients with proliferative diabetic retinopathy (PDR), 25% of patients were LTFU over a 4-year period, with researchers noting older patients, White and Asian patients, and patients with higher adjusted gross incomes more likely to return for follow-up care.[3] Another study tracking PDR follow-up rates found the LTFU rate as high as 52% at 1 year, and identified having government and private health insurance (as opposed to being a self-pay patient) as a risk factor for LTFU status.[4] Patients with PDR who received anti-VEGF therapy and are LTFU for at least 6 months may be at increased risk for developing a tractional retinal detachment (TRD) compared with LTFU patients who receive panretinal photocoagulation, with one study finding an incidence of TRD 10 times higher among anti-VEGF patients.[5] With cautionary statistics such as that in mind, eye care providers must educate patients that failure to follow up as directed could result in significant complications and vision loss.

The 2023 ASRS PAT survey asked US retina specialists about their most important metrics for success when employing anti-VEGF therapy for any disease (Figure 1).[1] A majority of US respondents cited vision improvements (81% of US respondents), longer treatment duration (66%), functional and anatomic stability (63%), and decreased treatment burden (51%) as their most important success metrics; the percentage of respondents who said that fewer injections could be used as a metric for success fell slightly under a majority (49%).

In short, eye care providers authorized to administer treatment want it all: reduced treatment burden that does not

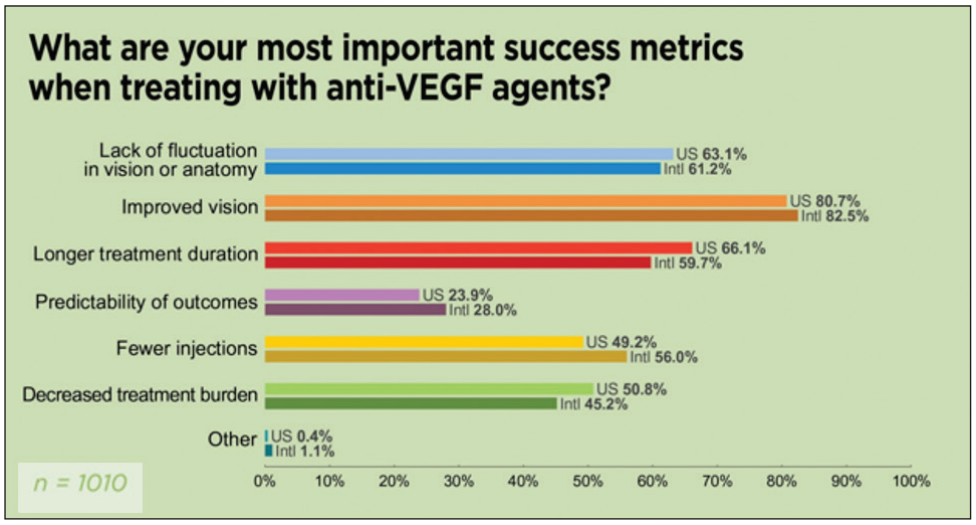

Figure 1. The 2023 ASRS PAT survey found that vision improvements, extended treatment duration, anatomic and functional stability, decreased treatment burden, and reduced number of injections were all popular metrics for success when using anti-VEGF therapy for retinovascular diseases.

sacrifice the visual and structural gains that first-generation anti-VEGF agents have realized with no increased safety risk. Three of the most recent innovations in retina therapy aim to accomplish those goals: faricimab, which is approved by the FDA for the treatment of DME[6]; aflibercept 8 mg, which is approved for the treatment of diabetic retinopathy (DR) and DME[7]; and brolucizumab, which is approved for DME.[8] All three of these therapies also have indications for non-diabetic eye diseases, but that is beyond the scope of this discussion.

Faricimab for DME

Faricimab is a bispecific antibody that inhibits both VEGF-A and angiopoietin-2 (Ang-2). The safety and efficacy of faricimab for the treatment of DME was assessed in the phase 3 Yosemite and Rhine studies, a pair of randomized, double-masked, active comparator–controlled phase 3 clinical trials.[9] Patients in those studies were randomly assigned to aflibercept 2 mg every 8 weeks after 5 monthly loading doses, faricimab every 8 weeks after 6 monthly loading doses, faricimab up to every 16 weeks after 4 monthly loading doses; this final arm was called the personalized treatment interval (PTI) arm, which is an approximation of real-world TAE regimens and permitted extension of the time between faricimab injections beginning in year 1, after loading doses were delivered, based on prespecified visual acuity and OCT thresholds. The primary endpoint for the Yosemite and Rhine studies was the mean change in BCVA from baseline as averaged over weeks 48, 52, and 56 (Figure 2).

The study met its primary endpoint.[9] At 2 years, patients in the faricimab arms demonstrated noninferior BCVA gains from baseline compared with the aflibercept 2 mg arm. Further, the faricimab arms showed comparable anatomic outcomes to the aflibercept 2 mg arm as measured by central subfield thickness (CST) reductions from baseline at 2 years.[10]

Durability was observed with faricimab treatment. In both trials, 78.1% of patients achieved at least Q12 week dosing at week 96, with a majority (60.0% and 64.5%) achieving 16-week dosing intervals (Figure 3).[10] Among those who achieved 16-week intervals in 1 year, 76% maintained that dosing schedule through 2 years.[10]

Faricimab was well tolerated through 2 years, and no instances of retinal vasculitis or occlusive retinal vasculitis were reported.[10]

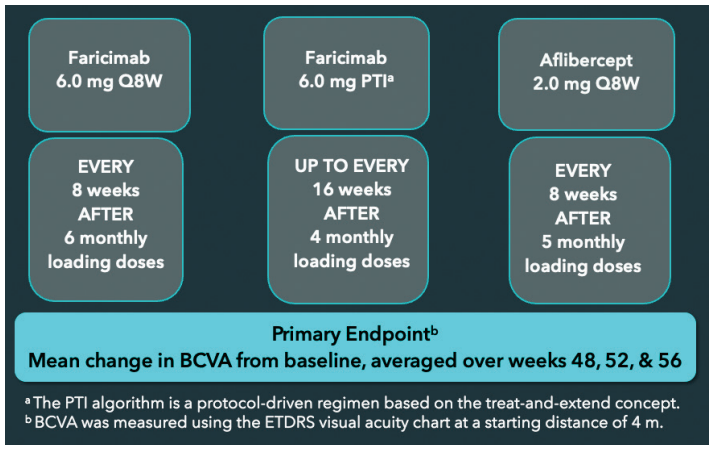

Figure 2. The study design for the phase 3 Yosemite and Rhine studies assessed faricimab dosed every 8 weeks, faricimab dosed on a PTI regimen up to every 16 weeks, and aflibercept 2 mg dosed every 8 weeks.

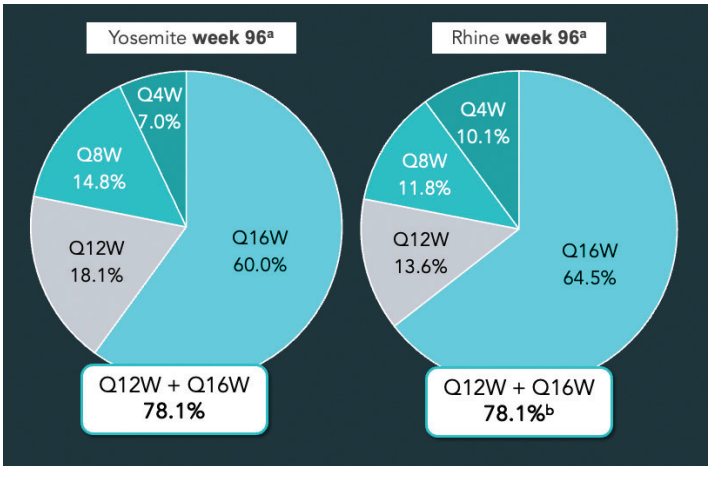

Figure 3. Among patients in the PTI arms, 78.1% in both Yosemite and Rhine achieved dosing intervals of at least 12 weeks, with a majority of PTI patients achieving 16-week treatment intervals. Adapted from: Lim JI, et al. Presented at: ARVO 2022; May 1-4, 2022; Denver, CO.

	Through 48 weeks (one year)			Through 96 weeks (two years)		
	aflibercept 2 mg 8-week regimen	aflibercept 8 mg 12-week regimen	aflibercept 8 mg 16-week regimen	aflibercept 2 mg 8-week regimen	aflibercept 8 mg 12-week regimen	aflibercept 8 mg 16-week regimen
Mean number of injections^	7.9	6.0	5.0	13.8	9.5	7.8
Mean observed BCVA improvement, letters	9.2	8.8	7.9	8.4	8.8	7.5
LS mean (SE) change from baseline, letters	8.7 (0.7)	8.1 (0.6)	7.2 (0.7)	7.7 (0.9)	8.2 (0.6)	6.6 (0.8)
Difference in LS mean (95% CI), letters		-0.6* (-2.3, 1.1)	-1.4† (-3.3, 0.4)		+0.5‡ (-1.6, 2.5)	-1.1§ (-3.3, 1.1)
Proportion of patients losing ≥15 letters, per LOCF	1.2%	2.1%	0.6%	3.6%	3.4%	1.2%

BCVA: best corrected visual acuity; LS: least squares; SE: standard error; LOCF: last observation carried forward
^Based on patients completing week 48 or 96 in the trial
*Noninferiority P -value: $P < .0001$
†Noninferiority P -value: $P = .0031$
‡Nominal noninferiority P -value: $P < .0001$
§Nominal noninferiority P -value: $P = .0044$

Figure 4. Outcomes data at weeks 48 and 96 in the Photon study. Note that the mean number of injections for the 16-week high-dose aflibercept arm was 5.0 at week 48 and 7.8 at week 96.

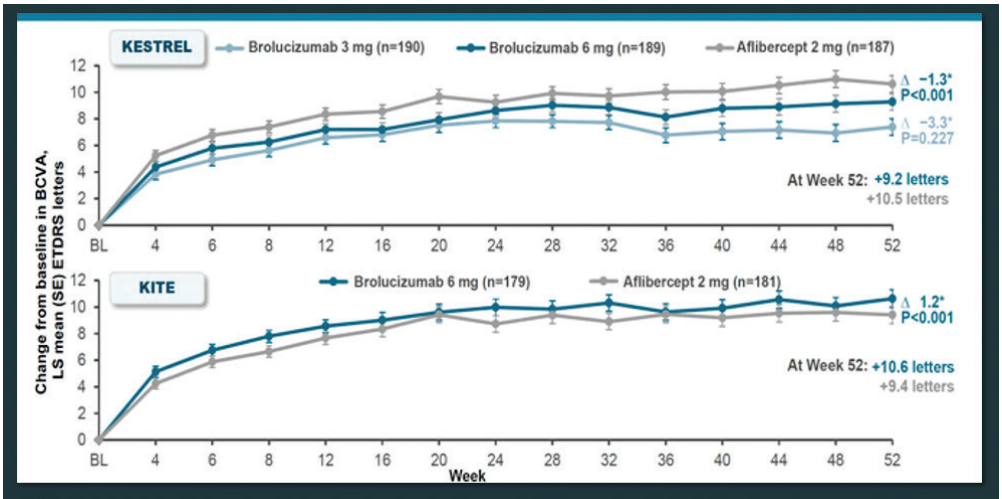

Figure 5. At week 52, patients who were randomly assigned to brolucizumab 6 mg dosed as infrequently as every 12 weeks in Kestrel and Kite had noninferior outcomes to patients who were dosed with aflibercept 2 mg every 8 weeks. Brown DM, et al. *Am J Ophthalmol.* 2022;238:157-172. Under a Creative Commons BY-NC-ND license.

High-Dose Aflibercept for DR and DME

High-dose aflibercept (8 mg) has a molar dose that is four times greater than that of aflibercept 2 mg. The safety and efficacy of high-dose aflibercept for the treatment of DME was assessed in the phase 3 Photon study.[11] Patients were randomly assigned to high-dose aflibercept every 12 weeks after 3 monthly doses, high-dose aflibercept every 16 weeks after 3 monthly doses, or aflibercept 2 mg every 8 weeks after 5 monthly doses. Patients in the high-dose aflibercept arms could have their intervals shortened during years 1 and 2, and could have their intervals extended during year 2.[11]

The primary endpoint for this noninferiority study was mean change in BCVA from baseline at week 48. The study met its primary endpoint at week 48, with mean observed BCVA improvement from baseline measured at 8.8 letters, 7.9 letters, and 9.2 letters in the high-dose aflibercept 12-week arm, high-dose aflibercept 16-week arm, and aflibercept 2 mg 8-week arm, respectively ($P < .01$).[11] At week 96, mean observed BCVA improvement from baseline measured at 8.8 letters, 7.5 letters, and 8.4 letters in the high-dose aflibercept 12-week arm, high-dose aflibercept 16-week arm, and aflibercept 2 mg 8-week arm, respectively ($P < .01$).[11] Other efficacy findings for both timepoints can be seen in Figure 4.

Anatomic findings were comparable among the three treatment arms in Photon, with reductions in CST ranging from 148 µm to 171 µm at week 48 and ranging from 144 µm to 187 µm at week 96.[11]

At week 96, 89% of patients randomized to high-dose aflibercept maintained at least 12-week dosing, and 84% of those randomized at baseline to 16-week intervals with high-dose aflibercept maintained that regimen at week 96.

Brolucizumab for DME

The safety and efficacy of brolucizumab for the treatment of DME was assessed in the randomized, double-masked, multicenter, active-controlled phase 3 Kestrel and Kite studies.[12] In Kestrel, patients were randomly assigned 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg; in Kite, patients were randomly assigned 1:1 to brolucizumab 6 mg or aflibercept 2 mg. The primary endpoint in both studies was BCVA change from baseline at week 52.

Patients who were assigned to the brolucizumab arms in Kestrel and Kite received five doses every 6 weeks before they were shifted to 12-week dosing; if prespecified criteria were met, they could be dosed as frequently as every 8 weeks. Patients in the aflibercept 2 mg arms received 5 monthly doses and were then shifted to fixed 8-week dosing.

At week 52, patients who received brolucizumab 6 mg showed noninferior visual outcomes compared with patients in the aflibercept 2 mg arms, which meant the study met its primary endpoint (Figure 5). After a series of real-world intraocular inflammation events with brolucizumab for the treatment of wet age-related

macular degeneration, some retina specialists have been hesitant to use this particular anti-VEGF agent.[13] Still, it is approved by the FDA, and patients that optometrists refer may initiate therapy with brolucizumab if a retina specialist feels that it fits their needs and the patient can be safely monitored for complications.

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12. 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;238:157-172.
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A POSSIBLE ROLE FOR HOME-BASED OCT IMAGING

Patients with diabetic macular edema (DME) only visit eye care providers periodically, meaning that we might catch changes to DME after they've been long present. But what if patients with DME could be identified and present closer to when treatment was needed? Home-based OCT may allow that.

A pilot study found that home-based OCT imaging is easy to use, and that more than 97% of images captured on the platform are of satisfactory quality.[1] A validated AI software automatically detects and quantifies intraretinal fluid and subretinal fluid at a 94% agreement rate with human graders.[2,3] If home-based OCT eventually earns both FDA clearance and wide adoption by eye care providers, it could lead to personalized treatment based on real-time anatomic changes.

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A Look at the Pipeline: Can Future Therapies Extend Duration Even Further?

JOSEPH SOWKA, OD, FAAO, DIPLOMATE

Various therapies are under investigation for the treatment of diabetic eye disease, many of them focusing on enhancing the duration of therapy.

PORT DELIVERY SYSTEM WITH RANIBIZUMAB

The Port Delivery System with Ranibizumab (PDS) is a surgically implanted reservoir that dispenses a continuous low dose of a customized formulation of ranibizumab. During a refill-exchange procedure, any remaining ranibizumab is removed from the PDS and a fresh payload is delivered.[1] Researchers evaluated the safety and efficacy of the PDS for two diabetic eye disease indications in two phase 3 trials: diabetic retinopathy (DR) without diabetic macular edema (DME) in the Pavilion study and with DME in the Pagoda study.

In Pavilion, patients with treatment-naïve DR without DME were randomly assigned 5:3 to PDS or control arms.[2] Patients in the PDS arm received a dose of intravitreal ranibizumab 1 month prior to PDS implantation and received a refill-exchange at week 36. Patients in the control arm were treated at investigator discretion with intravitreal ranibizumab at each monthly visit. Pavilion was a superiority study, with a primary endpoint of superior efficacy of the PDS compared with intravitreal ranibizumab treatment based on the proportion of patients with improvements in Early Treatment DR Study-DR Severity Score (ETDRS-DRSS) scoring of at least 2 steps at week 52.

Pavilion met its primary endpoint, with 80% of patients in the PDS arm experiencing a 2-step ETRDS-DRSS improvement compared with 9% of control patients ($P < .01$). The proportion of patients whose ETDRS-DRSS score worsened by 2 steps favored the PDS, with 2% of PDS patients experiencing a 2-step drop compared with 46% of patients in the control arm. No patients in the PDS arm needed supplemental treatment through 1 year.

The PDS was generally well tolerated. Further, a significantly higher percentage of patients in the control arm experienced vision-threatening complications or center-involved DME (CI-DME) at week 52 compared with the PDS arm. Specific statistics can be seen in Figure 1.

Researchers in the Pagoda study randomly assigned patients with DME who had undergone at least a 6-month treatment-free period in a 3:2 ratio to the PDS or to monthly intravitreal ranibizumab. Patients in each arm received 4 monthly doses,

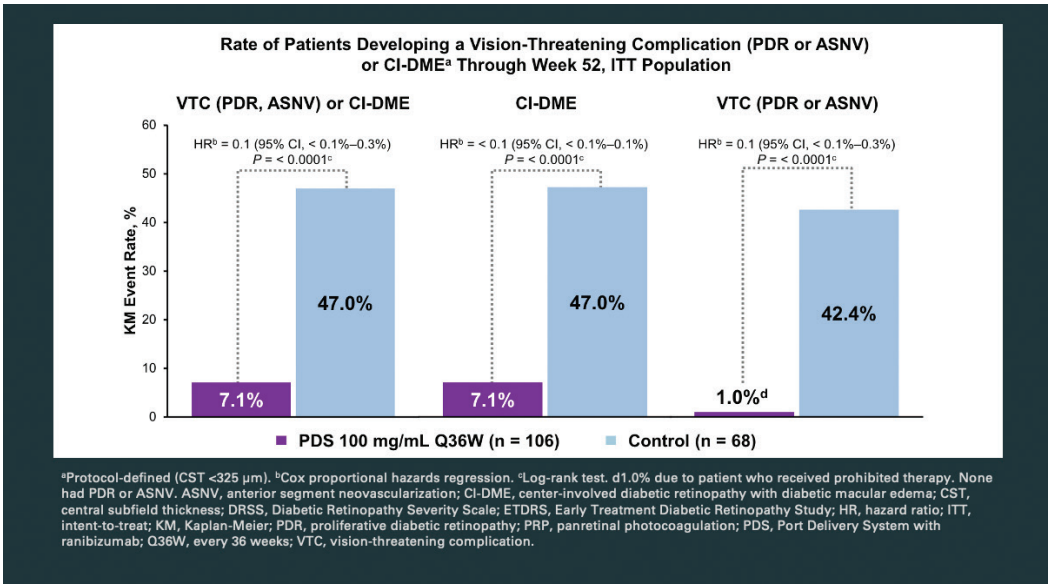

Figure 1. More patients in the control arm of Pavilion experienced a vision-threatening complication (VTC), defined as proliferative DR (PDR), anterior segment neovascularization (ASVN), or CI-DME. Adapted from: Pieramici D. Presented at Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2023 Virtual; February 10-11, 2023.

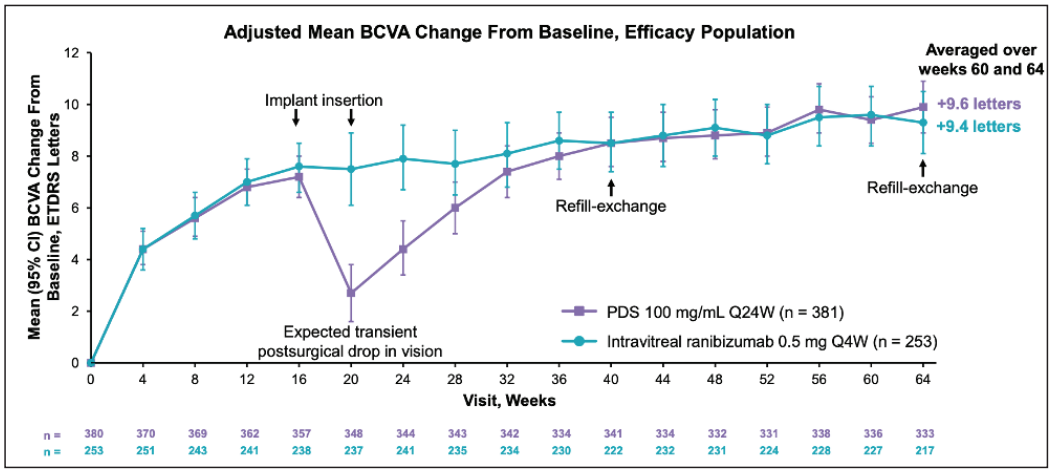

Figure 2. In Pagoda, patients with DME who received the PDS demonstrated similar visual gains to patients who received monthly ranibizumab injections. The drop in vision seen in the 3 months after PDS implantation was expected by the investigators. Presented at the ASRS Annual Meeting; July 28-August 1, 2023; Seattle, WA.

with those in the PDS arm receiving an initial PDS implantation at week 16 and a refill-exchange at week 40. The primary endpoint of the study was noninferiority of PDS compared with monthly intravitreal ranibizumab, based on change in BCVA score from baseline averaged over weeks 60 and 64.[3]

The study met its primary endpoint. Averaged over weeks 60 and 64, patients in the PDS arm gained mean 9.6 letters from baseline and patients in the monthly ranibizumab arm gained mean 9.4 letters from baseline. Patients in the PDS arm experienced a drop on letters gained after PDS implantation, as expected, but rebounded to pre-surgical vision approximately 12 weeks later (Figure 2). During the first refill-exchange interval (ie, between the first and second refill-exchange), 96% of patients did not require rescue therapy; during the second interval, 97% of patients did not require rescue therapy.[4]

GENE THERAPY

Gene therapy options for diabetic eye disease remain under investigation. Although exciting from a scientific standpoint, recent safety issues with gene therapy for diabetic eye disease have derailed some programs.

ABBV-RGX-314 is a recombinant adeno-associated viral vector (AAV) encoding a soluble monoclonal anti-VEGF.[5] In the phase 2 Altitude study, patients with DR without diabetic macular edema (DME) have received ABBV-RGX-314 via suprachoroidal delivery. Through year 1, the therapy has been well tolerated.[6] The study is ongoing.

ADVM-022 is an AAV encoding aflibercept that is delivered via intravitreal injection.[7] In 2021, following safety issues observed in the Infinity trial, the company announced that they would halt plans for further investigation in DME.[8]

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Real-World Cases From the Optometric Clinic

Discussions about eye care in a vacuum satisfy our academic instincts, but reviews of real-world cases transform conceptual discussions into practical ones. Here, Drs. Sowka and Chous share cases from their respective optometric practices, both of which illustrate the dynamics at play in patients with diabetic eye disease.

CASE 1

Case 1: Patient Lost to Follow-up After Initial Treatments

Joseph Sowka, OD, FAAO, Diplomate

A 62-year-old man with type 2 diabetes was referred to my clinic by his primary care provider following a report of 4 years of blurred vision OS. His medical history includes use of insulin, hypertension, hypercholesterolemia, seizure disorder, anemia, and end-stage renal disease that requires dialysis three times per week.

The patient's most recent ocular exam was 4 years ago. BCVA is 20/30- OD and 20/150 OS. A clinical examination revealed a grade-2 cataract OD and a grade-3 cataract OS. Scattered retinal and vitreous hemorrhages were observed OU (Figure 1). OCT imaging revealed diabetic macular edema (DME) in both eyes, and a tractional retinal detachment OS (Figure 2). No active proliferative diabetic retinopathy was observed.

I referred him to my practice's in-house surgeon. A retina specialist began treatment with ranibizumab OU, and the patient was instructed to return in 4 weeks. The patient was also cleared for cataract surgery, as the cataracts were advanced enough to realize visual disruption. The surgeons planned to assess the patient for retinal surgery after cataract surgery.

He never presented for cataract surgery. The patient was lost to follow up (LTFU) for a period of 2 years. Upon his return, the patient reported worsening vision. BCVA was 20/40 OD and count fingers at 6 feet OS. During the examination, it was unclear if the patient was still under the care of a primary care physician. The patient's fundus imaging did not depict many changes, but his cataracts had worsened significantly. The patient was referred for another cataract evaluation, which advised cataract surgery. He was again LTFU.

Given his history of noncompliance, a therapy with a longer duration could have helped this patient had he presented to the clinic for retinal care following cataract surgery.

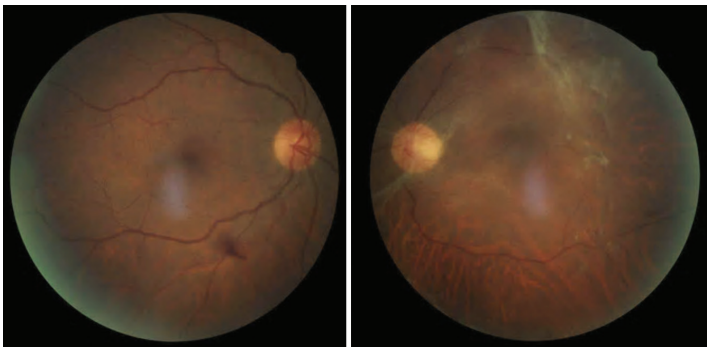

Figure 1. Bilateral hemorrhages were observed on color fundus photography in a patient with a long history of visual disruption. Despite the presence of disease in both eyes, the patient's BCVA was 20/30- OD. The patient's contralateral eye, however, had a 4-year history of blurred vision and 20/150 BCVA. Courtesy of Joseph Sowka, OD, FAAO, Diplomate.

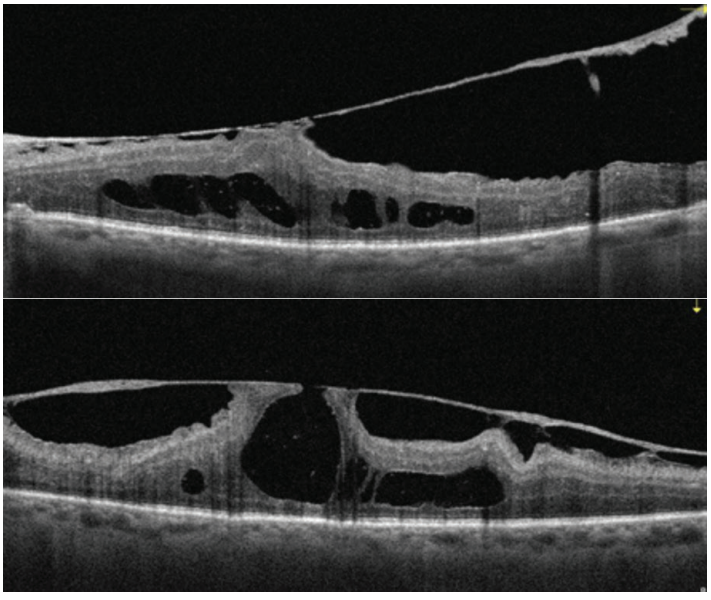

Figure 2. OCT imaging in the same patient depicted DME OU and a tractional retinal detachment OS. Courtesy of Joseph Sowka, OD, FAAO, Diplomate.

INSIGHTS FROM ROGER A. GOLDBERG, MD, MBA:

During my fellowship in Boston in the early 2010s, patients who lived in Massachusetts had been eligible for universal health coverage for several years. After years of primary care, early intervention, and prompt referral, it seemed like patients who lived in Massachusetts were less likely to present with extremely advanced cases of diabetic eye disease (namely, diabetic tractional retinal detachments). Many of the patients who presented with this severe level of disease, as seen in this case, were from the neighboring states, including Maine, New Hampshire, and Vermont, where universal care wasn't available. These are also more rural states where easy access to care may not have been present. This points to the interconnected nature of eye care: the greater the access to care, the earlier intervention can occur, and the more late-stage disease can be avoided.

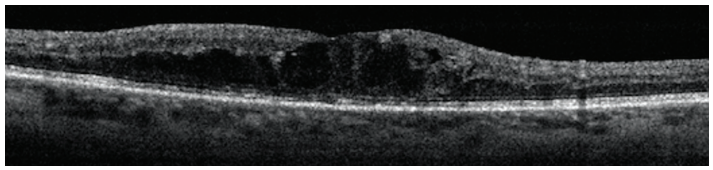

Figure 3. Upon presentation, a significant volume of retinal fluid was observed on OCT imaging. The patient's CST was 426 µm. She was diagnosed with moderate nonproliferative diabetic retinopathy and center-involved DME. Courtesy of A. Paul Chous, MA, OD, FAAO.

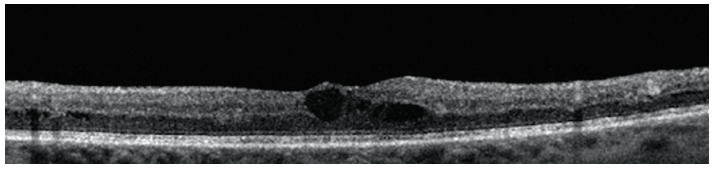

Figure 4. After 3 monthly injections of bevacizumab, fluid resolution was obvious on OCT. BCVA was 20/30 at this visit. Courtesy of A. Paul Chous, MA, OD, FAAO.

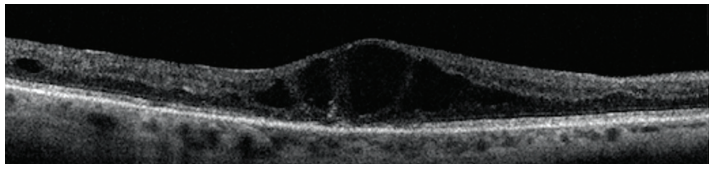

Figure 5. Although this patient presented for her first three bevacizumab injections, she was LTFU due to life circumstances. BCVA OD was 20/100 and recurrence of retinal fluid was observed on OCT. Courtesy of A. Paul Chous, MA, OD, FAAO.

CASE 2

Case 2: Illustrating the Need for More Durable Treatments

A. Paul Chous, MA, OD, FAAO

A 62-year-old Black woman with a 7-year history of type 2 diabetes presented to the clinic with complaints of reduced vision OD. Ocular examination revealed BCVA 20/50 OD, 18 mm Hg IOP OD, and central subfield thickness (CST) 426 µm OD. The patient's HbA1c was measured at 8.0% and reported being prescribed a continuous glucose monitor (CGM), but said she does not use it. She also reported use of a continuous positive airway pressure (CPAP) device for sleep apnea and a history of early diabetic kidney disease.

The patient was diagnosed with moderate nonproliferative diabetic retinopathy and center-involved DME (Figure 3). I sent a letter to her primary care provider with my findings, and referred her to a retina specialist. I also instructed her to make an appointment at my office at 2 months. I find that re-appointing patients to return to the optometric clinic at 2 months is a useful means by which to assure that they keep their visit with a retina specialist.

The patient returned to my clinic in 3 months for a follow-up refraction. She had received 3 monthly injections of bevacizumab, which was required by her insurance carrier before a branded drug could be administered. BCVA OD was 20/30 and her DME had significantly improved (Figure 4).

INSIGHTS FROM ROGER A. GOLDBERG, MD, MBA:

This patient would be a great candidate for a therapy that allows extended treatment intervals. Due to her status as a caretaker, the burden of retinal treatment is unusually high for this patient, because making it into the clinic for her own care may require her husband to sacrifice his care. In this scenario, the patient was unable to adhere to therapy. Patients shouldn't be penalized because they're providing care to others. In other words, we shouldn't blame the patient for nonadherence, but recognize that therapies that require frequent (eg, monthly) dosing may not be practical for all patients at all periods of time.

The patient was scheduled for a fourth bevacizumab injection in 8 weeks. After congratulating the patient on her diligent follow-up, I counseled her to continue with the recommended intravitreal injections, reminding her that she had a chronic condition that requires ongoing care.

The patient returned 3 months later (ie, a total of 6 months since her first presentation) and reported that she had missed her follow-up appointments with the retina specialist: As her husband's primary caretaker, she had to skip her own appointments as she drove him to his. Upon examination, I observed a recurrence of fluid and 20/100 BCVA OD (Figure 5).

I re-emphasized the importance of follow-up with the retina specialist for this patient, and strongly encouraged that she use her CGM. A growing body of evidence shows that CGM improves glycemic control in type 2 diabetes patients treated with insulin while also reducing the risk of hypoglycemia.[1,2] The latter point was made in light of data from the Fremantle Diabetes Study, which found that severe hypoglycemia was a major risk factor for losing vision during follow-up in patients with type 2 diabetes as a consequence of ophthalmic complications.[2]

I educated the patient that ocular therapies with longer duration of action are available, and recommended she speak with her retina specialist about them to learn more. Of course, I did not recommend a specific treatment—that is up to the retina specialist and the patient—but I did mention in my notes to the retina specialist that I spoke to the patient about longer duration treatments. This way, if the patient broaches the topic, the retina specialist can begin the conversation knowing that this is not the first time the patient has heard of options for extending treatment intervals without sacrificing efficacy. ■

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Diabetic Eye Disease Collaborative Care:
The Latest Treatment Innovations and Real-World Uses

COPE Release Date: March 22, 2024
COPE Expiration Date: March 31, 2025

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

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Review advances in current treatments for diabetic eye disease and nAMD	_____	_____	_____
Identify patients who may benefit from advances in the treatment paradigm for retinal vascular diseases	_____	_____	_____
Formulate strategies to identify and resolve barriers to optimal treatment outcomes for patients with nAMD and diabetic eye disease	_____	_____	_____
Summarize therapies for retinal vascular diseases that are in clinical development	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to formulate strategies to identify barriers to optimal treatment outcomes for patients with diabetic macular edema (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. A 55-year-old patient has a history of diabetes for 10 years. His most recent HbA1c was 8.4%, and his blood pressure was 138/78 mm Hg. He presents for a routine dilated eye exam during which moderate intraretinal microvascular abnormalities are observed in his right eye, with microaneurysms, intraretinal hemorrhages, and diabetic macular edema (DME) in his left eye. His VA is 20/20 in both eyes. What is the next best step to potentially maintain this patient's visual acuity?

a. Recommend a follow-up visit in 3 months
b. Recommend a follow-up visit in 3 months and educate the patient on the importance of a healthy diet and moderate exercise
c. Refer to a retina specialist for evaluation of potential treatment with intravitreal aflibercept 8 mg or faricimab
d. None of the above

3. Faricimab, approved for the treatment of wet age-related macular degeneration, DME, and macular edema following retinal vein occlusion, targets which of the following molecular facilitators of angiogenesis?

a. VEGF-A
b. VEGF-A and angiopoietin-2
c. VEGF-A and VEGF-B
d. VEGF-A and angiopoietin-1

4. A 66-year-old patient, who is a structural engineer, is currently receiving intravitreal aflibercept 2 mg injections for DME in both eyes. He has a history of diabetic kidney disease. His VA has improved from 20/50 to 20/25 after treatment with aflibercept 2 mg. Which of the following demographic or clinical factors is associated with the highest risk of loss to follow-up (LTFU) for this patient?

a. Diabetic kidney disease
b. Older age
c. High socioeconomic status
d. Improved visual acuity after anti-VEGF treatment

5. A 35-year-old patient presents with center-involving DME and 20/40 VA in her right eye. She states that she is a single mother and works two jobs to support her family. What is the next best step in this patient's care?

a. Schedule a 6-month follow-up visit
b. Refer the patient to a retina specialist for evaluation of potential treatment with intravitreal corticosteroid
c. Refer the patient to a retina specialist for evaluation of potential treatment with off-label intravitreal bevacizumab
d. Refer the patient to a retina specialist for evaluation of potential treatment with intravitreal faricimab

6. Which of the following statements is TRUE regarding the 52-week outcomes of patients with moderately severe to severe nonproliferative diabetic retinopathy in the Pavilion trial?

a. Port Delivery System with ranibizumab (PDS) Q36W was associated with significantly greater Diabetic Retinopathy Severity Scale (DRSS) worsening
b. PDS Q36W significantly lowered the rate of center-involving DME and vision-threatening complications
c. PDS Q36W was inferior to the control arm in a 2-step or more DRSS improvement
d. PDS Q36W significantly improved BCVA, with a trend toward improved central subfield thickness

7. Which of the following statements is TRUE regarding the key findings of the Yosemite and Rhine trials in patients with DME?

a. Faricimab had noninferior visual outcomes and comparable anatomic outcomes to aflibercept 2 mg over 2 years
b. Faricimab had better visual and anatomic outcomes compared to aflibercept 2 mg over 2 years
c. Faricimab had noninferior visual outcomes and comparable anatomic outcomes to panretinal photocoagulation over 2 years
d. Faricimab had better visual and anatomic outcomes compared to panretinal photocoagulation over 2 years

8. What percentage of patients with wet age-related macular degeneration or DME who were treated with faricimab achieved extended durability of Q12W or more dosing?

a. 20%
b. 40%
c. 60%
d. 80%

9. A 74-year-old patient with a history of diabetic eye disease for 5 years presents to your clinic. He states he has poor adherence to monthly anti-VEGF therapy because he is overwhelmed by other physician appointments with his dentist and endocrinologist. Which of the following intravitreal therapies is LEAST appropriate to treat his DME?

a. Ranibizumab
b. Faricimab
c. Aflibercept 8 mg
d. Brolucizumab

10. A 38-year-old Asian patient who is a dentist presents with proliferative diabetic retinopathy and a VA of 20/40 OU. Which of the following assessments and plans are most appropriate to manage this patient?

a. Patient is at a low risk for LTFU because of his age, race, and socioeconomic status; therefore, extended durability treatments are not necessary to consider
b. Patient is at a low risk for LTFU because of his age alone; however, extended durability treatments should always be considered
c. Patient is at a high risk for LTFU because of his age, race, and socioeconomic status; therefore, extended durability treatments should be considered
d. Patient is at a high risk for LTFU because of his age alone; therefore, extended durability treatments should be considered

11. All the following patients treated with anti-VEGF therapy for diabetic eye disease may benefit from switching to more durable anti-VEGF agents, EXCEPT?

a. A 65-year-old patient who lacks transportation
b. A 42-year-old patient with an improved VA of 20/20 after treatment
c. A 72-year-old patient with an improved VA of 20/30 after treatment
d. An 82-year-old patient with a left below-the-knee leg amputation

ACTIVITY EVALUATION

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

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

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

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

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

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

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

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

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

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

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

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

Additional comments:

_____

_____

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

_____

_____