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DEVELOPMENTS IN DIABETIC EYE DISEASE:
Optimizing Outcomes With Emerging Therapies

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DEVELOPMENTS IN DIABETIC EYE DISEASE: Optimizing Outcomes With Emerging Therapies

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This continuing education (CE) activity captures content from a virtual symposium.

Activity Description

This supplement summarizes a discussion on the unmet needs in diabetic eye disease, emerging treatments that may address those needs, and patient selection and education.

Target Audience

This certified CE activity is designed for optometrists.

Learning Objectives

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

- **Summarize** the current treatments and barriers to optimizing medical management of patients with diabetic eye diseases and neovascular age-related macular degeneration in clinical settings
- **Discuss** future therapies and their implications for patient outcomes
- **Identify** patients who may benefit from the next generation of retinal disease therapies

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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 discuss current and future therapies for optimizing medical management of patients with diabetic eye diseases (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 patients who may benefit from the next generation of diabetic eye disease therapies (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

A. 1
B. 2
C. 3
D. 4
E. 5

3. Which of the following statements regarding the relationship between anti-VEGF injections and visual outcomes in treatment of diabetic macular edema (DME) is TRUE?

A. Higher number of anti-VEGF injections correlates with better vision outcomes in DME
B. Lower number of anti-VEGF injections correlates with better vision outcomes in DME
C. Number of anti-VEGF injections does not correlate with vision outcomes in DME
D. It depends on the stage of diabetic retinopathy (DR)

4. All of the following are risk factors for patients with DR being lost to follow-up EXCEPT?

A. Older age
B. Younger age
C. Lower adjusted gross income
D. Hispanic/Native American/Pacific Islander race

5. A 56-year-old man with type 2 diabetes mellitus presents to your office for evaluation of blurry vision. On exam, you note diffuse dot blot hemorrhages in both eyes, exudates throughout the macula in both eyes, and center-involving DME in both eyes. The patient has never received any treatment for his DR before. Which of the following is the first-line agent for treatment of his DME?

A. Intravitreal VEGF blockage
B. Intravitreal corticosteroids
C. Focal laser treatment
D. Pars plana vitrectomy

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

A. Switch to intravitreal aflibercept
B. Switch to intravitreal bevacizumab
C. Trial of intravitreal corticosteroids
D. Maintenance on intravitreal ranibizumab

7. Faricimab is a first-in-class bispecific antibody that blocks_____

A. VEGF-A and Ang-2
B. VEGF-B and Ang-2
C. VEGF-A and Ang-1
D. VEGF-B and Ang-1

8. What is the lifetime risk of DR in patients with type 2 diabetes?

A. 10%-20%
B. 20%-30%
C. 40%-50%
D. 50%-60%

9. You are seeing a 78-year-old patient in your office for evaluation of blurred vision in both eyes. He travels 2 hours to reach your office. He has a history of anxiety and depression, and he is currently receiving chemotherapy for stage IV prostate cancer. He has DME in both eyes and you discuss treatment with anti-VEGF injections. All of the following may contribute to this patient's nonadherence, EXCEPT:

A. History of depression and anxiety
B. History of stage IV prostate cancer
C. Age of 78
D. High travel burden for injections

10. You are seeing a 56-year-old patient with DME. He is currently receiving intravitreal aflibercept every 4 weeks, and desires a more durable therapy. You discuss brolucizumab with him, and he asks about side effects. Which of the following statements is true, regarding side effects of brolucizumab?

A. Studies show an equal rate of intraocular inflammation between brolucizumab and aflibercept
B. Studies show a higher rate of intraocular inflammation with brolucizumab as compared to aflibercept
C. Studies show a higher rate of intraocular inflammation with aflibercept as compared to brolucizumab
D. There are no studies comparing intraocular inflammation between aflibercept and brolucizumab

11. A 58-year-old patient is maintained on monthly aflibercept for DME. She still has cystic intraretinal fluid on her OCT with a BCVA of 20/40, despite monthly treatment. Which of the following is the most reasonable treatment option for this patient?

A. Maintenance on intravitreal aflibercept
B. Switch to intravitreal bevacizumab
C. Schedule for pars plana vitrectomy
D. Switch to intravitreal faricimab

12. A 59-year-old patient presents to your office for evaluation. She has a history of moderate nonproliferative DR OU with DME OU and has been on multiple different anti-VEGF agents during the past 2 years. She complains of blurry vision OU, and on exam you note DME OU, OD>OS. You decide to treat her with six monthly injections of aflibercept. She returns 6 months later with no significant change in her vision or anatomy. All of the following are reasonable options, EXCEPT?

A. Continue using the same anti-VEGF injection treatment
B. Switch to another anti-VEGF agent
C. Initiate intravitreal corticosteroid treatment
D. Utilize a newer agent that offers anti-VEGF and anti-Ang-2

DEVELOPMENTS IN DIABETIC EYE DISEASE: OPTIMIZING OUTCOMES WITH EMERGING THERAPIES

PREVALENCE OF DIABETIC EYE DISEASE

It takes a village to care for a patient with diabetes, and optometry is on the front line of diabetic eye disease.

MARK T. DUNBAR, OD, FAAO

The global prevalence of diabetes has tripled over the past 20 years.[1] In 2019, 463 million people had diabetes, representing approximately 10% of the global population aged 20 to 79 years.[1] This number is expected to grow to 700 million by 2045. In the United States alone, more than 37 million individuals have diabetes.[2] Around 30% of patients with diabetes have diabetic retinopathy (DR), with 5% to 10% developing sight-threatening proliferative DR (PDR) and diabetic macular edema (DME), which are the main causes of vision loss in diabetes.[3] Given the growing global prevalence of diabetes, the prevalence of DR is also projected to increase to 242 million by 2045.[1] Unfortunately, 50% to 60% of patients with type 2 diabetes and up to 90% of patients with type 1 diabetes will eventually develop DR (Figure).[3]

Most patients with diabetes who are diagnosed with DR are unaware that they have the condition. In fact, up to 73% of participants in the 2005-2008 National Health and Nutrition Examination Survey were unaware that they had DR.[4] Once diagnosed, DR severity must be assessed to identify a patient's risk of progression to vision loss. The Early Treatment of Diabetic Retinopathy Study (ETDRS) demonstrated that patients with mild and moderate nonproliferative DR (NPDR) have a 5% and 12% 1-year risk, respectively, of developing PDR.[5] As such, these patients are observed every 9 to 12 months, depending on other risk factors. Not surprisingly, the 1-year risk of progression to PDR increases to 52% when patients present with severe NPDR.[5] Even a 1-step or more progression on the ETDRS retinopathy severity scale over a 4-year period was found to be clinically meaningful in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.[6] These patients were almost six times more likely to develop PDR and four times more likely to develop clinically significant macular edema over the next 6 years.[6]

Patients with severe NPDR are observed much more closely because of the increased risk of progression to PDR. As the disease advances, it can be difficult to discern the nuances that separate severe NPDR from PDR (ie, intraretinal microvascular abnormalities vs neovascularization elsewhere). For these reasons, it is best to refer these patients to retina specialists who may be better equipped to manage the increased risk of complications of PDR, such as vitreous hemorrhage, tractional retinal detachment, and

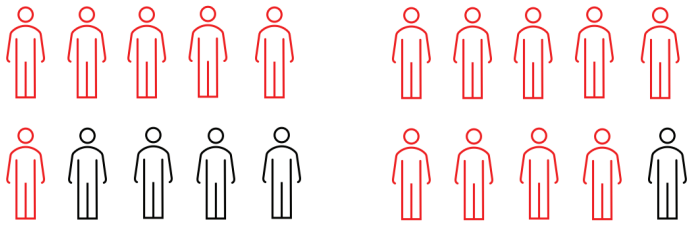

Figure. Fifty percent to 60% of patients with type 2 diabetes and up to 90% of patients with type 1 diabetes will eventually develop DR.[3]

"Around 30% of patients with diabetes have DR, with 5% to 10% developing sight-threatening PDR and DME, which are the main causes of vision loss in diabetes.[3]"

—Mark T. Dunbar, OD, FAAO

vision loss. What's more, retina specialists are starting to treat patients with severe NPDR before they progress to PDR.

Finally, optometrists need to be on the lookout for DME, which can develop at any stage of DR. While it is more likely to occur as the disease progresses,[6,7] patients with mild to moderate disease may also present with DME. These days, with optical coherence tomography, we can diagnose and categorize these patients, particularly those with center-involved DME who are at higher risk of vison loss, in a much timelier manner.

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CURRENT TREATMENTS FOR DIABETIC EYE DISEASE

During the last decade, the treatment paradigm for diabetic macular edema has changed tremendously, allowing us to prevent further vision loss and even recover some lost vision.

VEERAL S. SHETH, MD, MBA, FASRS, FACS

While intravitreal VEGF blockade is the gold standard treatment for most patients with diabetic macular edema (DME), particularly those with center-involved DME (CI-DME), we also use intravitreal corticosteroids and focal macular laser photocoagulation in select patients.

Intravitreal anti-VEGF therapy—namely ranibizumab,[1,2] aflibercept,[3] and bevacizumab[4]—has shown strong evidence of efficacy in treating CI-DME in clinical trials. While ranibizumab and aflibercept are approved by the FDA, bevacizumab continues to be used off-label. More recently, brolucizumab,[5] a novel anti-VEGF agent, and faricimab,[6] a bispecific antibody that inhibits VEGF-A and Ang-2, were also approved for the treatment of patients with DME. Broadly speaking, anti-VEGF injectables are superior to laser photocoagulation and intravitreal corticosteroids, and have a good ocular and systemic safety profile.

The phase 3 RISE and RIDE trials were landmark studies that changed the treatment paradigm for DME.[2] They compared patient cohorts receiving monthly injections of ranibizumab 0.3 mg, 0.5 mg, or sham. At 24 months, patients receiving ranibizumab gained, on average, 12 letters compared to those receiving sham injections, who only gained 2.5 letters. Importantly, after 2 years, patients in the sham arm were allowed to receive ranibizumab injections and, although they gained 4.5 letters at the 3-year timepoint, their vision gain did not approach the gains maintained by those in the ranibizumab arms.[2] Our learnings from these trials were two-fold: one, that ranibizumab was able to improve and preserve vision especially compared to the standard of care at the time; and two, that late intervention resulted in some permanent vision loss that could not be recovered. Additionally, vision improvements in these trials corresponded with structural improvements as seen on optical coherence tomography, ie, mean central foveal thickness was significantly lower in patients receiving ranibizumab.

"Broadly speaking, anti-VEGF injectables are superior to laser photocoagulation and intravitreal corticosteroids, and have a good ocular and systemic safety profile."

—Veeral S. Sheth, MD, MBA, FASRS, FACS

After ranibizumab was shown to be effective in DME, another anti-VEGF agent, aflibercept, was evaluated against laser photocoagulation in the phase 3 VIVID and VISTA trials on monthly and bimonthly dosing regimens.[3] Similar to RISE and RIDE, both regimens of aflibercept demonstrated significantly greater vision gains compared to the standard of care by year 2, further reinforcing the efficacy of targeting the VEGF pathway. Given that there were three anti-VEGF agents available to treat DME (including off-label bevacizumab), the Diabetic Retinopathy Clinical Research Network (DRCR.net), which is funded by the National Institutes of Health and National Eye Institute, conducted the PROTOCOL T trial to compare all three agents head-to-head. By year 2, all three therapies showed an improvement in BCVA from baseline. Notably, patients with baseline BCVA between 20/32 to 20/40 had similar 2-year BCVA outcomes regardless of the agent used. However, in those with baseline BCVA of 20/50 or worse, aflibercept, ranibizumab, and bevacizumab delivered gains of 18.1, 16.1, and 13.3 letters, respectively. Similarly, aflibercept also produced greater mean reductions in central subfield thickness, compared to ranibizumab and bevacizumab. In all, aflibercept, ranibizumab, and bevacizumab demonstrated stepwise improvements in visual and anatomic outcomes.

Other studies have also noted that switching patients from ranibizumab and/or bevacizumab to aflibercept, particularly in cases of persistent DME, was safe and did confer some additional benefit.[7-10] However, all patients respond differently to different anti-VEGF agents, so results across switching studies can vary. Most recently, favorable short-term outcomes were shown when switching patients with treatment-resistant DME on aflibercept to faricimab.[11] Finally, the DRCR.net PROTOCOL AC trial recently demonstrated that patients with DME can be initiated on bevacizumab, which is a more affordable treatment option, and then

switched to aflibercept without a significant difference in visual outcomes compared to those initiated and maintained on aflibercept monotherapy, during a 2-year period.[12] However, it should be noted that 70% of eyes in the bevacizumab-first group were switched to aflibercept due to a suboptimal response.[12]

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REAL-WORLD OUTCOMES FOR DIABETIC EYE DISEASE

The excellent gains obtained in randomized clinical trials are not reflected in real-world outcomes.

JACQUELINE THEIS, OD, FAAO

In addition to the increasing number of options now available to treat diabetic macular edema (DME), an evolution of dosing regimens has occurred. The first clinical trials used a fixed monthly regimen, and over time this has evolved to bimonthly, quarterly, prn (on an "as needed" basis once the retina is dry), or treat-and-extend (TAE) regimens.[1] In particular, the TAE regimen has been shown to reduce the treatment burden in comparison to both prn and monthly regimens.[2-4]

However, the excellent gains obtained in randomized clinical trials are not reflected in real-world outcomes. An evaluation of more than 13,000 patients with new-onset DME in the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) registry, who were diagnosed from 2013 to 2016, showed that those who initiated anti-VEGF treatment within the first 28 days received a median of only four injections in the first year.[5] Moreover, 74.5% of patients received no treatment in the first 28 days after diagnosis.[5] A more recent retrospective analysis of the IRIS registry, including patients initiating anti-VEGF treatment in 2015 to 2019, found that the mean number of injections decreased from 3.9 to 2.9 and the injection intervals increased from 10.0 to 12.3 weeks, year-on-year over 6 years, regardless of baseline BCVA.[6]

Uniformly, across all real-world studies, the number of anti-VEGF injections correspond to visual outcomes. In 2018, Ciulla et al conducted a retrospective analysis of a large database of aggregated, de-identified electronic medical records from a geographically and demographically diverse sample of patients. Within the first year of treatment, they found a linear relationship between the number of letters gained and mean number of injections, after two injections. Approximately 50% of eyes received six or fewer injections. Generally, patients receiving more injections benefitted from greater improvement in vision.[7] This trend was also noted up to year 5; however, the mean visual acuity change from baseline decreased from +4.6 letters to +3.1 letters from year 1 to year 5.[8]

The 5-year global, real-world, prospective, open-label LUMINOUS study, which assessed the efficacy of ranibizumab 0.5 mg in 1,063 treatment-naïve patients with DME, also showed that the change in visual acuity was dependent on injection frequency. Notably, patients who received a mean of four or fewer injections saw significantly lower vision gains than those receiving five or more injections (+0.5 vs +6.9 letters, respectively).[9]

Overall, these real-world data are striking. They clearly demonstrate that patients are not receiving the number of injections needed to initiate and maintain optimal vision gains. Some of the reasons associated with nonadherence to treatment include poor understanding (or education) of the need for continued therapy to maximize benefits, loss of mobility, transportation issues (long distances or dependence on caregiver), fear of injections, fear of receiving a poor prognosis, vacation/travel, systemic and/or mental health comorbidities, and direct and indirect (eg, time off work, childcare) costs of treatment (Table).[10]

TABLE. FACTORS LINKED TO NONADHERENCE

Lack of knowledge about anti-VEGF therapy benefits
Loss of mobility
Lack of transportation
Fear of injections
Fear of receiving a poor prognosis
Vacation or travel
Comorbid depression or anxiety
Serious comorbid illness taking priority
High out-of-pocket costs

"Instead of simply asking patients whether they are receiving injections or seeing a retina specialist, we can push further on the timing of their last injection, ask when the next visit is scheduled, and encourage them to attend."

—Jacqueline Theis, OD, FAAO

Studies have shown that approximately one-quarter of patients with DME, who are receiving anti-VEGF treatment, are lost to follow-up (LTFU), ie, more than12 months between appointments.[11] This is unacceptable given the real-world data demonstrating that at least five injections are needed annually to see vision gains.[9] Some of the factors associated with LTFU were decreasing baseline visual acuity, average adjusted gross income less than $75,000, and non-White race.[11] Perhaps unsurprisingly, a separate study found that the mean visual acuity significantly worsened when patients become LTFU (>6 months between appointments).[12] However, visual acuity can recover to pre-LTFU levels in as soon as 3 months after reinitiating treatment.[12] These data are very encouraging and highlight an opportunity for optometrists to step up. Instead of simply asking patients whether they are receiving injections or seeing a retina specialist, we can push further on the timing of their last injection, ask when the next visit is scheduled, and encourage them to attend. For example, some patients with diabetes may experience a stroke and may miss appointments with their retina specialists while in the intensive care unit. In our practice, as soon as these patients are discharged, we'll try to return them to routine anti-VEGF injections because their DR will have likely progressed.

Overall, real-world data demonstrate the unmet needs in retina, namely reducing the treatment burden and ameliorating under-treatment by either improving efficacy and/or durability or targeting a different mechanism of action.[13]

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NEW AND EMERGING THERAPIES TO EASE THE TREATMENT BURDEN AND IMPROVE OUTCOMES

Brolucizumab and faricimab were recently approved for the treatment of patients with diabetic macular edema.

CARL D. REGILLO, MD, FACS

Our current treatment options for diabetic macular edema (DME) produce excellent outcomes, but the anti-VEGF agents we have been using have limited durability. Consequently, when patients are nonadherent to treatment, we cannot achieve or maintain maximal vision gains over time. While some intravitreal corticosteroid treatments are longer lasting, these drugs are associated with an increased risk of elevated IOP and cataract progression and are often relegated to second-line or combination treatment with anti-VEGF agents. Therefore, there is a real need for new therapies that improve long-term vision outcomes.

In the past year, brolucizumab and faricimab received FDA approval for the treatment of center-involved DME. In the phase 3 KITE and KESTREL trials, brolucizumab 6 mg dosed every 8 or 12 weeks was compared with aflibercept 2 mg dosed every 8 weeks, after their respective loading doses given every 6 and 4 weeks, respectively.[1] Both trials showed that brolucizumab achieved the primary endpoint of noninferiority in mean change in BCVA from baseline at 52 weeks.[1] These vision gains were maintained over 100 weeks.[2] Brolucizumab and aflibercept also produced comparable reductions in central subfield thickness (CST); however, the KITE trial showed that brolucizumab may have an enhanced drying effect with a greater degree of CST reduction, on average, compared to aflibercept. This may be pertinent in DME as enhanced drying could correlate with better vision. Moreover, there were a greater proportion of subjects with an effectively dry macula (CST <280 µm) in the brolucizumab arms of both trials and with fewer injections required than in the aflibercept arm. As the KITE trial was designed to allow flexible dosing intervals up to 16 weeks, 47.5% of patients were able to achieve intervals of at least 12 weeks.[2] These results

"Faricimab is unique because of its dual mechanism of action. By binding to both VEGF-A and Ang-2, it not only inhibits vascular leakage and neovascularization, but also enhances vascular stability and reduces inflammation.[3]"

–Carl D. Regillo, MD, FACS

suggest increased durability with brolucizumab. Whether this will be borne out in clinical practice remains to be seen.

The safety profile of brolucizumab has previously been an issue when treating patients with neovascular age-related macular degeneration (nAMD). While the rates of adverse events were mostly comparable across both KITE and KESTREL for brolucizumab and aflibercept, the rates of intraocular inflammation (IOI) were higher with brolucizumab, particularly in the KESTREL trial, ie, 4.2% versus 1.1%.[2] This imbalance is noteworthy because some cases of IOI were severe and had associated retinal vasculitis and occlusions, which led to retinal damage and vision loss in some patients.[2] As these adverse events are not typically seen with other anti-VEGF agents, brolucizumab is, at present, considered second-line treatment to be used if a patient may benefit from an enhanced drying effect.

Faricimab, the other agent that was recently approved for DME, is unique because of its dual mechanism of action. By binding to both VEGF-A and Ang-2, it not only inhibits vascular leakage and neovascularization, but also enhances vascular stability and reduces inflammation.[3] The identical phase 3 YOSEMITE and RHINE trials compared faricimab 6 mg against aflibercept 2 mg, with a primary endpoint of mean change in BCVA from baseline at approximately 1 year.[4] Faricimab was trialed at two dosing regimens, ie, every 8 weeks after a loading phase, similar to aflibercept, or a personalized treatment interval (PTI), which comprised of a shorter loading phase followed by variable dosing up to 16 weeks individualized per patient.[5] The PTI regimen was designed to capitulate the treat-and-extend approach taken in clinical practice.

Faricimab met the primary endpoint in both YOSEMITE and RHINE with noninferiority in visual outcomes, which were maintained over 100 weeks.[4] It also tended to have a better drying effect, ie, CST reduction, across both trials compared to aflibercept. Additionally, a significantly higher proportion of patients in the faricimab arms did not have intraretinal fluid. Most impressively, 60% to 65% of patients achieved q16w dosing in the PTI arm, with 76% of those who achieved this interval by week 52 maintaining the interval up to week 96. Across both faricimab arms, 79% of those who achieved at least 12-week intervals at week 52 maintained these intervals up to 96 weeks without having to undergo interval reductions below q12w. These outcomes were noted with a median of three injections in year 2 in the PTI arm compared to five injections for both the q8w faricimab and aflibercept arms. The safety profile of faricimab appeared comparable to that of aflibercept.[4] In all, faricimab delivered similar visual gains and safety to aflibercept, but with potentially better drying ability and durability. Therefore, it promises to reduce the treatment burden and produce better anatomic outcomes.

There are a few emerging therapies that are still currently being evaluated in clinical trials, all with the aim of improving durability, including KSI-301, aflibercept 8 mg, the port delivery system (PDS), and gene therapies (Table).

KSI-301 is an anti-VEGF conjugated to an optically inert, high molecular weight biopolymer, designed to enhance drug retention in the vitreous humor. Patients in the phase 1b trial were given 3 monthly loading doses, followed by rescue treatments as needed (mean of one injection administered over week 8 to 52), and demonstrated a mean 7.6-letter vision gain and 136-µm reduction in CST at week 52.[6] Up to 69% of patients were able to achieve a 6-month or longer treatment interval.[6] While not necessarily an indication of what might transpire in the real world, these results hint at the possible greater durability of the drug compared to those used in practice and provided a rationale for designing the phase 3 program. The GLEAM and GLIMMER trials are evaluating KSI-301 dosed variably every 2 to 6 months, after three loading doses, in patients with DME.[7,8] In February 2022, it was reported that KSI-301 did not meet the primary endpoint in the phase 3 nAMD trial, possibly due to the trial design that only allowed 3- to 5-month dosing.[9] The broader dosing range in the DME trials may deliver more promising results, which are due in 2023.

High-dose aflibercept (8 mg), which is four times the FDA-approved dose (2 mg), was assessed in the 1-year phase 2/3 PHOTON trial in DME at 8q12 and 8q16 dosing, after the loading phase, against aflibercept 2q8 dosing.[10] The study met its primary endpoint of noninferior visual acuity gains, with 91% and 89% of patients maintaining q12w and q16w dosing on aflibercept 8 mg, respectively.[10] Again, these proportions may not reflect what we will see in the real world, but we are getting closer to achieving those goals with aflibercept 8 mg, which may be approved sometime within the next 12 months or so.

TABLE. EMERGING DME TREATMENTS

KSI-301
High-dose aflibercept (8 mg)
Port delivery system (PDS)
Gene therapy

"Gene therapy is currently the most innovative approach to sustained delivery. It involves introducing a viral vector encoding an anti-VEGF protein into retinal cells and turning them into 'biofactories' capable of producing the anti-VEGF molecule."

–Carl D. Regillo, MD, FACS

The PDS and gene therapies are examples of truly sustained delivery of anti-VEGF treatment. In the nAMD ARCHWAY trial, the PDS demonstrated a durability of at least 6 months in 95% to 98% of patients.[11] It is an intraocular reservoir device, surgically implanted into the eye wall and filled with 20 µL of a high concentration of ranibizumab in an OR. Refill-exchange procedures are then performed in the clinic using a special refill-exchange needle. As a surgical procedure, the PDS has a unique side effect profile, many of which were seen in the nAMD trials, including conjunctival erosions and retractions, vitreous hemorrhage, retinal detachment, and endophthalmitis. While the PDS does have many advantages, including 90% patient preference for the implant over monthly injections, it does also have trade-offs.[11] In October 2022, the manufacturer announced a voluntary recall of the implant (but not the refill-exchange needle or ranibizumab vial), due to concerns of the septum (seal) of the implant failing after refill-exchange procedures.[12] While there is currently no medical need to remove devices that have already been implanted or halt refill-exchange procedures, new implantations have been paused. The PAGODA and PAVILION trials, which are evaluating the PDS in patients with DME and nonproliferative diabetic retinopathy (NPDR) without DME, respectively, are currently in the follow-up phase with results expected in 2023.[13,14] The manufacturer hopes to begin distribution of the PDS, after making modifications, within the next 12 months.[12]

Gene therapy is currently the most innovative approach to sustained delivery. It involves introducing a viral vector encoding an anti-VEGF protein into retinal cells and turning them into "biofactories" capable of producing the anti-VEGF molecule. Both ADVM-022 and RGX-314 are viral vectors encoding an aflibercept-like and ranibizumab-like protein, respectively. Currently, ADVM-022 is delivered by intravitreal injection; however, this route is more likely to induce IOI, which is one of the reasons why the DME (but not the nAMD) trial was halted.[15] RGX-314 is being delivered either through a subretinal injection, which requires a vitrectomy, or a suprachoroidal injection. The latter is an in-office procedure using a proprietary injection needle. Currently, the phase 2 ALTITUDE trial in diabetic retinopathy (DR) is utilizing this approach.[15] Of those patients with NPDR at baseline, 43% demonstrated at least a 2-step-improvement in Diabetic Retinopathy Severity Scale score at 3 months.[16] This is on-par with the improvements observed with frequent and regular intravitreal ranibizumab or aflibercept injections over 1 to 2 years.

Overall, given the promise of emerging second-generation treatments for diabetic eye disease, new agents that were recently approved (brolucizumab and faricimab), and existing highly effective and safe first-generation anti-VEGF agents, we are in a good position to not only reduce the treatment burden for our patients but also improve outcomes. The future of treatment for DR and DME is bright.

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PATIENT CONSIDERATIONS FOR EMERGING THERAPIES

Drs. Dunbar, Sheth, and Regillo discuss why patient education is critical.

Veeral S. Sheth, MD, MBA, FASRS, FACS: When I think about patients that would benefit the most from these innovations in diabetic retinopathy (DR) and diabetic macular edema (DME), I primarily consider two types of patients. The first is the incomplete responder. These are patients who are receiving frequent anti-VEGF therapy but still have persistent retinal fluid. For example, in PROTOCOL T, 41%, 64%, and 52% of eyes receiving aflibercept, bevacizumab, and ranibizumab

received at least one session of rescue focal/grid laser treatment due to DME persisting for longer than 6 months without improvement.[1] Therefore, a sizeable portion of treated eyes respond suboptimally to anti-VEGF monotherapy. The second type of patient is what we may call a "frequent flyer," or patients who require treatment every 4 weeks or so for adequate disease control. Understandably, these patients eventually experience injection fatigue, which is when compliance issues may arise. Being able to reduce this fatigue with more durable treatment options would go a long way toward making sure patients adhere to treatment. However, it's important to select patients who understand that increased durability is not a hall pass for skipping appointments. Having these patient conversations, conveying the benefits and the risks, can be tricky.

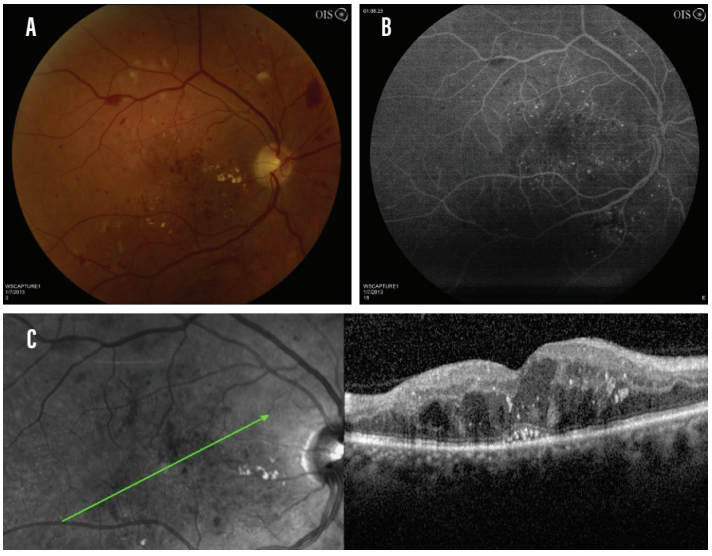
Mark T. Dunbar, OD, FAAO: Absolutely. It starts with education. Oftentimes, a retina specialist at a high-volume clinic may not necessarily have the time to provide the level of education that is sometimes needed for patients to realize that they will potentially require treatment for the rest of their lives. I think we as optometrists can take on this role.

When patients are referred to us by their endocrinologist or primary care physician, we can make sure they understand why we're seeing them, what the disease is, why they need a dilated eye exam, and what we're looking for. I'll start by describing that DR affects the small blood vessels in the eye, causing them to leak or bleed. By showing them their fundus photographs, fluorescein angiograms, or even optical coherence tomography (OCT) images, they can then visualize these changes in their own eyes. I'll then explain that we can closely monitor the status of these blood vessels through annual eye exams and, certainly when needed, control the build-up of fluid with regular treatment. I'll also reiterate what they will have heard from their other diabetes care team members, ie, how maintaining good blood pressure and glycemic control is beneficial, and how that impacts the eye.

For patients with proliferative DR (PDR) or DME, I'll impress upon them that even though their vision is currently compromised, there are treatments available. The diagnosis does not necessarily mean they will lose vision or go blind.

I recently saw a patient who had seen a retina specialist 2 years prior for mild nonproliferative DR (NPDR), but she had not followed up after that visit. The disease had slightly progressed in that time. When I explained that she had DR, she seemed surprised to hear the diagnosis and then distraught when she finally understood what that meant. This is not an uncommon story, but it really highlights the need for proper disease education.

As optometrists, we do have to strike a delicate balance of how much information we provide. We know that the idea of intravitreal injections can be intimidating. A lot of people have a fear of needles and that alone may prevent the patient from returning. I will first try to communicate the hope that treatment can maintain or improve vision. When they start asking further questions, I'll then convey that it is an intravitreal injection, which is well-tolerated and relatively pain-free. I'll always finish by referring them to a retina specialist, as appropriate, and stressing the importance of compliance with follow-ups and any treatments.



Courtesy of Carl D. Regillo, MD, FACS.

Figure 1. Baseline fundus photograph (A), fluorescein angiogram (B), and OCT images (C) of the right eye of a 58-year-old patient with type 2 diabetes and 20/100 vision.

A TYPICAL CASE OF DME

Carl D. Regillo, MD, FACS: This case is a 58-year-old phakic man with type 2 diabetes. The baseline fundus photograph and fluorescein angiogram both show severe NPDR and a myriad of leaking microaneurysms, but no neovascularization (Figures 1A, 1B). He presented with 20/100 vision in the right eye and had experienced blurry vision for approximately 3 months. The fellow eye was unaffected and had good visual acuity. The OCT image of the right eye showed moderately severe center-involved DME (Figure 1C).

At the time that the patient presented at my clinic, only ranibizumab and off-label bevacizumab were used for DME treatment. He was initiated on monthly ranibizumab injections and demonstrated good adherence to treatment over the next several months. This was also borne out in his OCT scans, which showed slow but steady reductions in edema associated with similarly slow improvements in visual acuity (Figure 2).

By month 7, the patient had received eight ranibizumab injections. The center of the macula had some residual fluid and his VA had drastically improved to 20/30. At this point in the treatment course, what would you do?

Dr. Sheth: Since the first 7 months went well, I'd say the next 6 months would depend on the patient. If the patient were willing and there was still some disease activity, I'd have pushed further to a completely dry macula, and 20/25 or 20/20 VA. However, it's also highly likely that the patient may want some reprieve after this rigorous schedule of injections. An alternative

Courtesy of Carl D. Regillo, MD, FACS.

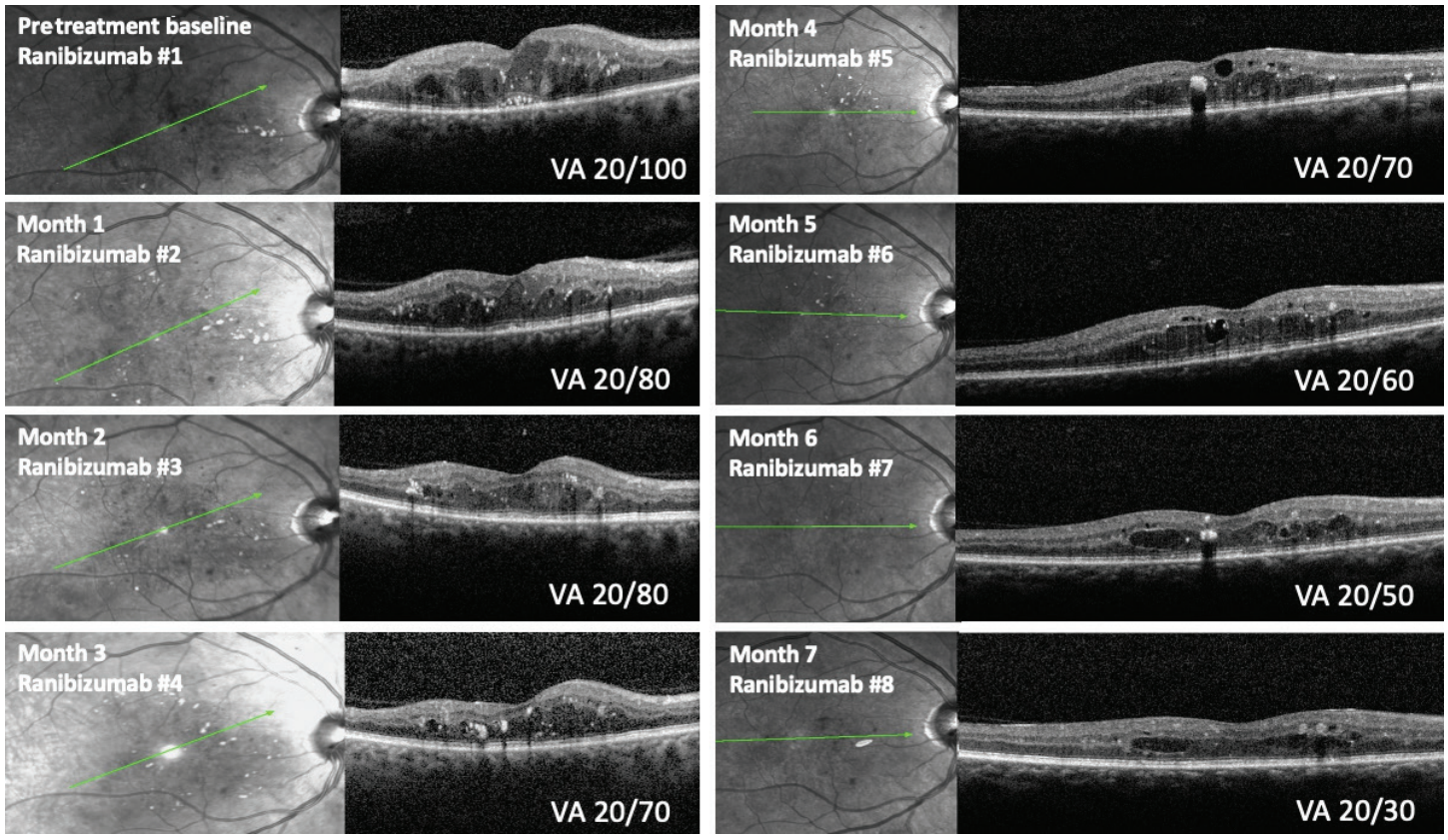


Figure 2. Treatment course of intravitreal ranibizumab injections over 7 months in a patient with DME. Visual acuity and macular thickness demonstrate slow improvement over time with strict adherence to monthly injections.

strategy may then be to try to extend the treatment interval to every 2 months. We could also consider several other options, but my first would be to get better outcomes on this dosing regimen and with this drug.

Dr. Regillo: You're right about there being many options. There is no right answer in this case. We could try switching to aflibercept, which was shown to have a better drying ability in PROTOCOL T; however, by year 2, aflibercept did not maintain superiority over ranibizumab.[1] If we were unable to extend the treatment interval with ranibizumab, we could try faricimab with the hopes of achieving greater durability. Over time, as the level of retinopathy improves in many patients on regular anti-VEGF therapy, and we grow more confident in the reduced risk of progression to PDR, we can test the waters further by stopping treatment and seeing how the disease responds.

Dr. Dunbar: This case is very typical of the challenges we currently face in DME. The hope with the newer approved therapies, and those in the pipeline, is that we're working towards achieving a considerable reduction in treatment burden with similar or better visual and anatomic outcomes compared to the anti-VEGF therapies we use today. This patient is still of working age so reducing that burden is a welcome prospect for him.

Dr. Regillo: Definitely. We all have to work together as a team to keep these patients on board and coming back to the office for evaluation and treatment, because we're all aware of the issues surrounding injection fatigue, nonadherence, and becoming lost to follow-up. It's one thing for the patient to receive treatment and see immediate gains, but entirely another for those who receive regular treatments but improve slowly, as with this case. Many patients in this scenario may believe that they are not having much benefit, become discouraged, and lose motivation to attend appointments. We need to drive home the point that the treatment response will be different for each patient and that, ultimately, treatments don't work if patients don't receive them. ■

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DEVELOPMENTS IN DIABETIC EYE DISEASE:
OPTIMIZING OUTCOMES WITH EMERGING THERAPIES

COPE Release Date: January 1, 2023
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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
Summarize the current treatments and barriers to optimizing medical management of patients with diabetic eye diseases and neovascular age-related macular degeneration in clinical settings	_____	_____	_____
Discuss future therapies and their implications for patient outcomes	_____	_____	_____
Identify patients who may benefit from the next generation of retinal disease therapies	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to discuss current and future therapies for optimizing medical management of patients with diabetic eye diseases (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 patients who may benefit from the next generation of diabetic eye disease therapies (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

A. 1
B. 2
C. 3
D. 4
E. 5

3. Which of the following statements regarding the relationship between anti-VEGF injections and visual outcomes in treatment of diabetic macular edema (DME) is TRUE?

A. Higher number of anti-VEGF injections correlates with better vision outcomes in DME
B. Lower number of anti-VEGF injections correlates with better vision outcomes in DME
C. Number of anti-VEGF injections does not correlate with vision outcomes in DME
D. It depends on the stage of diabetic retinopathy (DR)

4. All of the following are risk factors for patients with DR being lost to follow-up EXCEPT?

A. Older age
B. Younger age
C. Lower adjusted gross income
D. Hispanic/Native American/Pacific Islander race

5. A 56-year-old man with type 2 diabetes mellitus presents to your office for evaluation of blurry vision. On exam, you note diffuse dot blot hemorrhages in both eyes, exudates throughout the macula in both eyes, and center-involving DME in both eyes. The patient has never received any treatment for his DR before. Which of the following is the first-line agent for treatment of his DME?

A. Intravitreal VEGF blockage
B. Intravitreal corticosteroids
C. Focal laser treatment
D. Pars plana vitrectomy

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

A. Switch to intravitreal aflibercept
B. Switch to intravitreal bevacizumab
C. Trial of intravitreal corticosteroids
D. Maintenance on intravitreal ranibizumab

7. Faricimab is a first-in-class bispecific antibody that blocks_____

A. VEGF-A and Ang-2
B. VEGF-B and Ang-2
C. VEGF-A and Ang-1
D. VEGF-B and Ang-1

8. What is the lifetime risk of DR in patients with type 2 diabetes?

A. 10%-20%
B. 20%-30%
C. 40%-50%
D. 50%-60%

9. You are seeing a 78-year-old patient in your office for evaluation of blurred vision in both eyes. He travels 2 hours to reach your office. He has a history of anxiety and depression, and he is currently receiving chemotherapy for stage IV prostate cancer. He has DME in both eyes and you discuss treatment with anti-VEGF injections. All of the following may contribute to this patient's nonadherence, EXCEPT:

A. History of depression and anxiety
B. History of stage IV prostate cancer
C. Age of 78
D. High travel burden for injections

10. You are seeing a 56-year-old patient with DME. He is currently receiving intravitreal aflibercept every 4 weeks, and desires a more durable therapy. You discuss brolucizumab with him, and he asks about side effects. Which of the following statements is true, regarding side effects of brolucizumab?

A. Studies show an equal rate of intraocular inflammation between brolucizumab and aflibercept
B. Studies show a higher rate of intraocular inflammation with brolucizumab as compared to aflibercept
C. Studies show a higher rate of intraocular inflammation with aflibercept as compared to brolucizumab
D. There are no studies comparing intraocular inflammation between aflibercept and brolucizumab

11. A 58-year-old patient is maintained on monthly aflibercept for DME. She still has cystic intraretinal fluid on her OCT with a BCVA of 20/40, despite monthly treatment. Which of the following is the most reasonable treatment option for this patient?

A. Maintenance on intravitreal aflibercept
B. Switch to intravitreal bevacizumab
C. Schedule for pars plana vitrectomy
D. Switch to intravitreal faricimab

12. A 59-year-old patient presents to your office for evaluation. She has a history of moderate nonproliferative DR OU with DME OU and has been on multiple different anti-VEGF agents during the past 2 years. She complains of blurry vision OU, and on exam you note DME OU, OD>OS. You decide to treat her with six monthly injections of aflibercept. She returns 6 months later with no significant change in her vision or anatomy. All of the following are reasonable options, EXCEPT?

A. Continue using the same anti-VEGF injection treatment
B. Switch to another anti-VEGF agent
C. Initiate intravitreal corticosteroid treatment
D. Utilize a newer agent that offers anti-VEGF and anti-Ang-2

ACTIVITY EVALUATION

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

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

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

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

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

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

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

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

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

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

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

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

Additional comments:

_____

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

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

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MODERNOPTOMETRY