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nAMD Collaborative Care: Current Challenges and Potential Solutions

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nAMD Collaborative Care: Current Challenges and Potential Solutions

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

Activity Description

This supplement summarizes a panel discussion about collaborative care for patients with retinal disease, with a focus on neovascular age-related macular degeneration (nAMD).

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 neovascular age-related macular degeneration (nAMD) (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. On a scale of 1 to 5 (with 1 being never and 5 being always), please rate how often you are able to resolve barriers to optimal treatment outcomes for patients with nAMD.

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

3. Which of the following statements about the number of anti-VEGF injections and vision outcomes in nAMD is TRUE?

A. Higher number of anti-VEGF injections correlates with better vision outcomes in nAMD
B. Higher number of anti-VEGF injections correlates with worse vision outcomes in nAMD
C. The number of anti-VEGF injections does not correlate with vision outcomes in nAMD
D. The number of anti-VEGF injections correlates with vision outcomes only in vision that is > 20/40 at diagnosis

4. You are evaluating an 88-year-old patient with nAMD. His OCT shows cystic intraretinal fluid overlying a fibrovascular pigment epithelial detachment. He lives more than 75 miles away from the nearest retina practice and has limited mobility. Which of the following options represents the best therapeutic option for this patient?

A. Intravitreal bevacizumab monthly
B. Intravitreal ranibizumab monthly
C. Intravitreal corticosteroid therapy
D. Longer acting therapy such as faricimab or port delivery system with ranibizumab

5. Which of the following characteristic of patients with nAMD receiving anti-VEGF therapy increases risk of being lost to follow-up?

A. Caucasian race
B. Young age (50-60 years)
C. Medicaid insurance
D. Medicare fee-for-service insurance

6. You are evaluating a 78-year-old patient with newly diagnosed nAMD. She is well versed in the current clinical trials and is excited about starting anti-VEGF therapy for her condition. She asks if she can expect a similar number of yearly injections as noted in the trials. What is the best response for this patient?

A. Real-world patients with nAMD receive fewer injections than patients in clinical trials
B. Real-world patients with nAMD receive more injections than patients in clinical trials
C. Real-world patients with nAMD receive equal injections to patients in clinical trials
D. Real-world patients > 70 years old with nAMD receive more injections than patients in clinical trials

7. According to the literature, real-world injection data indicate that patients with nAMD received _____ injections per year:

A. 3 to 4.5
B. 4 to 5.7
C. 6 to 7.6
D. 9 to 10.5

8. You are evaluating a 67-year-old male with nAMD on monthly ranibizumab. He is well controlled on this medication with a dry OCT; however, he cannot be extended beyond 4 weeks. He has previously failed both aflibercept and faricimab. He finds his monthly injections burdensome and wishes for a more durable option. Which is the most reasonable option for this patient?

A. Switch to monthly aflibercept
B. Switch to monthly bevacizumab
C. Switch to monthly faricimab
D. Consider the port delivery system with ranibizumab if available

9. What is the mechanism of action of OPT-302?

A. Blocks all VEGF isoforms
B. Blocks VEGF-A and VEGF-B
C. Blocks VEGF-C and VEGF-D
D. Block VEGF-A and VEGF-C

10. ADVM-022 is a novel therapeutic meant to deliver a gene encoding for an anti-VEGF protein into the eye. How is this medication delivered?

A. Oral pill
B. Subretinal injection
C. Intravitreal injection
D. Intramuscular injection

11. RGX-314 can be delivered into the eye by which of the following methods?

A. Subretinal injections/suprachoroidal injection
B. Intracameral injection
C. Topical suspension
D. Intravitreal injection

12. A 72-year-old woman presents to your office with a diagnosis of nAMD OD. She has a prior history of receiving bevacizumab and aflibercept and is currently on monthly aflibercept treatment. She has persistent cystic intraretinal fluid and subretinal fluid despite monthly aflibercept injections. Her retina specialist switches to brolucizumab OD. One month later, she complains of floaters and blurred vision since her last brolucizumab injection and you note 10 cells/hpf in her anterior chamber, with no other symptoms or signs. What is the next best step in management?

A. Vitreous tap and inject for presumed endophthalmitis
B. Start prednisolone drops four times daily for anterior segment inflammation
C. Start acyclovir for presumed herpetic infection
D. Start moxifloxacin drops for presumed infection

nAMD Collaborative Care: Current Challenges and Potential Solutions

Intravitreal anti-vascular endothelial growth factor (VEGF) injections for neovascular age-related macular degeneration (nAMD) were a paradigm-shifting treatment when they first became available to us nearly 2 decades ago. However, these first-generation agents were not without their limitations—an intense treatment burden being the primary one. Indeed, several studies have reported that real-world injection frequencies and outcomes fall short of those observed in clinical trials.[1-7] *While the reasons for this discrepancy are many, the fact remains that a large portion of our patients do not achieve optimal outcomes. During a recent vitual symposium, Drs. Dunbar, Steen, and I discussed how recent additions to the nAMD armamentarium are starting to improve durability and the other agents we may expect to see in clinics in the not-too-distant future.*

– Roger A. Goldberg, MD, MBA, Program Chair

Editor's Note: *This panel discussion took place prior to the approval of 8-mg aflibercept.*

"The risk of developing late AMD increases from 0.2% in those age 55 to 64 years to 13% in those older than 85 years."

– Mark T. Dunbar, OD, FAAO

BARRIERS TO OPTIMAL TREATMENT OUTCOMES

Mark T. Dunbar, OD, FAAO: According to the American Optometric Association, optometrists deliver 85% of primary eye health care in America, with our practices covering 99% of the population.[8] This isn't surprising given the multiple points of entry into the eye care system, ie, private practices, commercial retail, OD/MD comanagement, and hospital settings. Optometry is, undoubtedly, on the front lines of patients with macular degeneration. We see a lot of these patients, and we are oftentimes the first to diagnose AMD.

We know we have an aging population. Every day, approximately 10,000 people become 65 years old in the United States.[9] That's a staggering number. A recent study estimated that 18.34 million individuals in the United States, older than 40 years, have early-stage AMD and 1.49 million have late-stage AMD, ie, either geographic atrophy (GA) or nAMD.[10] We see these patients in our practice on a routine basis and know that they go on to suffer significant vision loss. AMD is most prevalent in those of White (non-Hispanic) descent, compared to Black or Hispanic individuals, and in older people, ie, those older than 65 years. The risk of developing late AMD increases from 0.2% in those age 55 to 64 years to 13% in those older than 85 years.[11] This is not an insignificant proportion of patients.

When we think about the evolution of treatments for nAMD, laser photocoagulation was the standard for several years. It obliterated the neovascular complex but, of course, left a permanent scotoma. The hope was that the scar that developed from the laser would be smaller than what would have occurred from the natural course of the disease and, in turn, result in better visual outcomes. However, in both instances, the visual outcome was not always as hoped, especially if the macular neovascularization involved the fovea.

In comparison, anti-VEGF treatments were a real breakthrough. For the first time in history, patients were seeing a significant improvement in their visual acuity. The downside, of course, was that these agents required monthly injections to generate a successful outcome. This was a tremendous treatment burden, not only on the patients and their caregivers, but also on our retina specialist community. When aflibercept became available, it was approved for an 8-week regimen. The community then started considering whether doses could be given "as needed"/*pro re nata* (prn) or with a "treat-and-extend" (TAE) regimen, ie, treat more frequently early on, monitor these patients carefully, and slowly extend their treatment intervals, where possible.

Regardless of the regimen, it became clear that these first-generation agents just had poor durability. They weren't potent enough and there was a limit to how long we could extend patients before fluid recurrence. Moreover, some patients had persistent edema that would not resolve even with monthly injections. It's difficult to sustain this kind of schedule and patients develop burnout.

The LATAR study was a single practice, real-world Australian study looking at 293 eyes with nAMD that received anti-VEGF therapy for 10 years.[12] Patients averaged about 58 injections in this time, likely having more frequent injections early on and fewer injections in the later years. As we would expect, central macular thickness decreased significantly from 355.5 µm to 264.2 µm, and patients gained an average of 9 letters in their first year from a median baseline of approximately 20/60. However, by year 10, these initial gains were mostly lost and patients had a final improvement of 3 letters from baseline.[12] This speaks to the poor durability of these medications. If

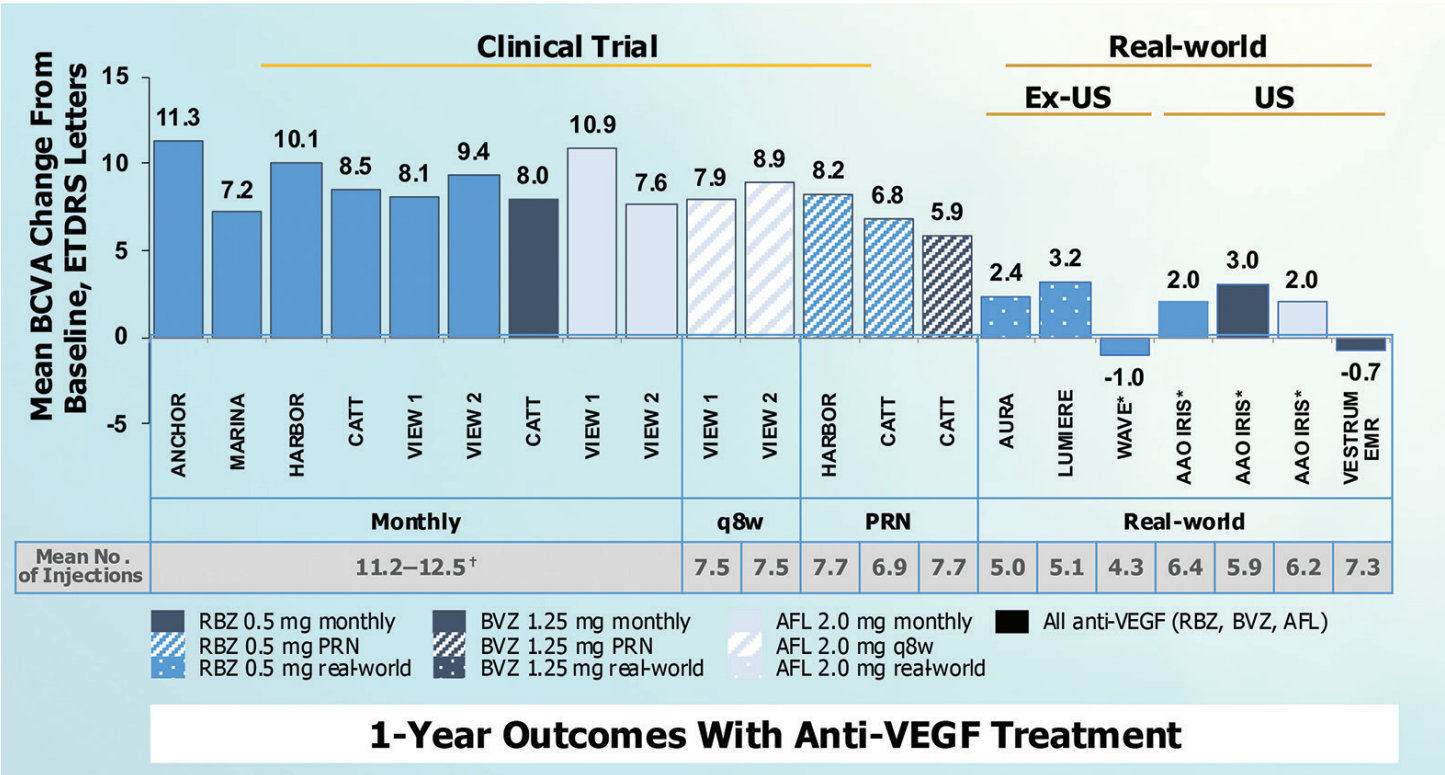

Figure 1. Real-world vision outcomes fall short of those seen in clinical trials.

patients don't get an injection every single month, they will typically end up losing vision.

The proportion of eyes with 20/40 VA or better increased significantly from 29% at baseline to 35% at 10 years.[12] The flipside, however, is that nearly 70% of patients have worse than 20/40 VA at diagnosis and the majority remain that way after 10 years of injections. We use 20/40 VA as a benchmark because that's functional vision from a quality-of-life perspective. That's the ability to drive a car. That's the ability to read newsprint. If you have 20/40 vision, you're able to do most things. Although there is clearly a treatment benefit, it's much harder to regain vision when you start with worse vision at treatment initiation. In fact, the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS) registry showed that the mean visual acuity at conversion in the real world is 20/83.[13] If you start with that level of vision, you never really catch up to those that are caught earlier.

When we hear that real-world vision outcomes are lower than those seen in clinical trials, we have to remember that in sponsored clinical trials, treatments are free and patients are given access to a lot of resources to ensure they stay on regimen. We typically see gains of 10 or 11 letters (Figure 1). This doesn't happen in the real world. Similar to the Australian study,[12] patients in the IRIS registry gained between 2 and 3 letters (Figure 1), which is far worse than what we see in randomized clinical trials.

Why does this treatment gap exist? It's likely a combination of several factors. Patients may not grasp that anti-VEGF injections are chronic and must be given regularly. I remember a clinical trial patient at Bascom Palmer celebrating her 100th anti-VEGF injection—this was someone who was motivated enough and able to make those visits. Let's not forget most of these patients are older, have loss of mobility, lack of transportation, rely on family/friends to take them to appointments, have a fear of injections, face high out-of-pocket costs (for those on a fixed income), and have comorbidities that all play a role in the eventual loss of treatment adherence.

Recently, study investigators used the IRIS registry to investigate the rate of loss-to-follow-up (LTFU) among 156,327 patients with nAMD who received anti-VEGF therapy between 2013 and 2015 and had follow-up data up to 2019.[14] By definition, LTFU meant that patients had no follow-up within 12 months since their last injection. The LTFU rate was one in nine, meaning that at least 89% of patients were able to maintain relatively more frequent follow-up, which is pretty good. As we might expect, patients who were LTFU lost an average of 3.2 ± 21 letters between their first and last treatments. They were also significantly less likely to have 20/40 VA or better compared to those who were not LTFU (36% vs 43%, respectively) and more likely to lose more than 5 letters in their treated eye (37% vs 32%, respectively). The study noted that the odds of being LTFU were higher in older patients (eg, LTFU rate was highest in those 81-84 years old), Black/African American individuals (vs White), and those with Medicaid insurance (vs Medicare fee-for-service and private insurance).[14] While the data may not be all that surprising, it supports the need for continued treatment and demonstrates some of the barriers to optimal outcomes.

Roger A. Goldberg, MD, MBA: I think sometimes the phrase "lost to follow-up" implies it's the patient's fault, but all those risk factors are just reflections of real life. Older people have more medical comorbidities. They're more dependent on others for transportation. There are probably social determinants that also impact how easy it is for them to get into clinic to receive care. Instead of thinking of LTFU as something that the patient has done wrong, we should reframe it as a limitation of this first generation of therapies that just aren't that durable. So, the impact of "loss to follow-up" is all the more significant. Any therapy that needs to be administered on a monthly or every-other-month basis for the patient's lifetime will have these limitations.

Dr. Dunbar: Absolutely. If we could extend treatment to every 3 to 4 months, the outcomes may be much better because patients are less reliant on having to come in to see their retina specialist.

This experience with anti-VEGF is not uniquely American. The 2-year, real-world AURA study found that patients across the UK, Netherlands, Germany, France, and Italy all see vision gains from baseline within the first 2 to 3 months, but during the next 2 years, these gains are lost.[15] In some countries, patients returned to baseline within a year and continued to lose vision up to year 2. Comparing the mean of five injections administered in year 1 across the study and the 2.2 injections administered over year 2, we can see that undertreatment may be one of the reasons for these vision losses.

We saw a similar trend in the United States in a retrospective study of a database of almost 50,000 eyes that received anti-VEGF injections between 2012 and 2016.[4] The FDA guidance for ranibizumab and aflibercept suggests that patients should ideally receive eight to 12 injections for adequate disease control. However, more than half of the eyes in this study received seven or fewer injections. So, already, in year 1 we see that undertreatment is a problem. Patients receiving six or fewer injections lost between 0 and 3 letters. Those who received seven or more injections saw vision gains between 1 and 5 letters, which is still more modest than what we have typically seen in clinical trials.[4] Over and over, the data show that if the recommended number of injections aren't administered, patients will end up with suboptimal visual outcomes. Again, this speaks to the poor durability of the first-generation of anti-VEGF drugs.

We touched on this earlier, but one of the reasons for suboptimal outcomes is compliance. Almost 80% of patients and caregivers report disruptions to their routine on the day before, day of, and day after anti-VEGF treatment.[16] A multi-national qualitative study including the United States, Canada, France, Germany, Italy, and Spain found an interesting disconnect between what patients and retina specialists see as drivers for adherence to treatment. Seventy percent of patients considered their relationship with their doctor to be the primary driver for staying on treatment, whereas only 15% of retina specialists had the same belief. This may not be surprising. Many of our retina specialists are seeing more than 70 to 80 patients a day. Their priority is to treat the eye. How well can you foster a relationship in the small period of time they have available? But patients clearly value it. There was also a disconnect between the greatest barriers to adherence–67% of patients reported it to be side effects such as pain/discomfort/irritation, whereas 71% of retina specialists believed it to be logistical parameters such as travel.[16]

Dr. Goldberg: This study was fascinating. Forty-five percent of retina specialists believed patient education on treatment to be the primary driver of adherence to treatment.[16] To me, this speaks to the doctor-patient relationship as well. If we took the time to emphasize the importance of maintaining treatment at every almost visit, this would probably improve the doctor-patient relationship from the patient's perspective and be addressing the retina specialist's concern around patients getting enough education on the importance of ongoing treatment. But it is certainly interesting to highlight the differences between what the patient thinks and what the physician thinks. This would be a great place for optometry and retina to work together and emphasize the same messages.

Jessica Steen, OD: I agree. When patients come to our optometry offices, we should be thinking about how we can make each other's lives easier. Part of that is supporting what the retina specialist is doing by managing the patient's expectations around the chronicity of therapy and related visual outcomes.

Dr. Dunbar: No doubt. The suboptimal outcomes we see may also be because of an incomplete response to anti-VEGF therapy. The CATT, VIEW1, and VIEW2 trials all had a subset of patients (between 19.7% and 67.4%) who had persistent fluid on OCT even after 1 to 2 years of anti-VEGF therapy.[17,18] Along with poor durability, it's possible that these agents just aren't potent enough for some patients or they develop a 'resistance' to anti-VEGF therapy over time. We might see this resistance due to AMD genetic risk variants, neovascular architectural differences, or simply the involvement of other disease mechanisms. The VEGF pathway is certainly not the only one at play. Misdiagnosis may also play a role. In fact, I had an elderly patient yesterday who had received multiple anti-VEGF injections but still had persistent fluid. As it turned out, she may have been misdiagnosed as having nAMD instead of central serous chorioretinopathy.

There are likely other reasons for suboptimal outcomes, but the bottom line is that it is probably unrealistic to expect our patients in the real-world to behave like those in the clinical trials and expect similar outcomes. At least, not until the treatments themselves become better, more durable.

THE TRANSITION TO GREATER DURABILITY

Dr. Steen: The American Society of Retinal Specialists sends out an annual survey to its US and international society members to understand some of the differences and trends in practice patterns and opinions. When it comes to the biggest unmet need

in nAMD therapeutics, most respondents agree that longer lasting therapies are the No. 1 unmet need and are actively seeking improved outcomes for a significant proportion of their patients. In the past few years, advances in nAMD therapies have included faricimab, the Port Delivery System (PDS) with ranibizumab, and brolucizumab.

Faricimab

The VEGF pathway is a tried-and-true mechanism of controlling retinal vascular disease but it's not the only mechanism. Faricimab is a bispecific antibody, which targets VEGF-A as well as angiopoietin-2 (Ang-2).[19] Both angiopoietin-1 (Ang-1) and Ang-2 bind to the Tie2 receptor. Ang-1 activates Tie2, which leads to downstream reduction of inflammation and vascular leakage, and improved vascular stability. However, when Ang-2 binds to Tie2, the receptor is not activated, leading to an overall increase in inflammation and reduced stability. In nAMD, Ang-2 levels are upregulated.[19] Therefore, we can see how binding and inhibiting the actions of both VEGF-A and Ang-2 would be beneficial in the context of nAMD.

TENAYA and LUCERNE were the two international phase 3 trials that evaluated faricimab against aflibercept for the treatment of nAMD.[20] More than 1,300 treatment-naïve patients aged 50 years and older were recruited and randomized 1:1 to receive either treatment. Aflibercept, in its 2 mg FDA-approved dosage, was administered as three monthly loading doses, followed by 8-weekly treatment. Faricimab was administered as four monthly loading doses, followed by 8- to 16-week intervals, using a protocol-driven TAE regimen.[21] If patients had active disease (as determined by the investigator) at week 20, they were switched to an 8-weekly program thereon through to week 60. If patients evaluated at 24 weeks showed disease activity, they were maintained on a 12-weekly program, but if no disease activity was determined, patients were continued on a 16-weekly program. The second year of the program allowed for a more real-world TAE approach in all patients receiving faricimab.

The primary endpoint was noninferiority in mean change in best-corrected visual acuity (BCVA) from baseline averaged over weeks 40, 44, and 48 (depending on treatment intervals) to aflibercept.[20] Faricimab met this endpoint. The study design allowed for a few interesting comparisons during the loading period. During weeks 4, 8, and 12, those treated with faricimab had a greater reduction in central subfield thickness (CST) on OCT and slightly improved visual acuity compared to those treated with aflibercept. As we might expect with faricimab's flexible dosing schedule, individuals in the faricimab group received fewer injections over the trial period versus those in the aflibercept group. In terms of durability, about 80% of faricimab-treated patients were able to maintain at least 12-week intervals. This is an agent that is efficacious both in terms of BCVA and CST, with greater durability. The safety data for faricimab was comparable to that of aflibercept, with no new or unexpected safety signals.[20]

Dr. Dunbar clearly outlined how visual outcomes in clinical trials are not comparable to those in real life. The TRUCKEE study was designed to evaluate how real-world patients fared on faricimab.[22] Almost 90% of patients in this study were treatment-experienced, ie, had received other anti-VEGF therapy before receiving faricimab; only a small proportion were treatment-naive. After at least three faricimab injections, there was a significant reduction in the number of treatment-experienced individuals who had intraretinal or subretinal fluid and pigment epithelial detachment, ie, people who had active disease. So, these are individuals with a completely dry inner and outer retina. However, with this being a real-world study, only two safety signals were reported. A single case of infectious endophthalmitis was successfully treated with intravitreal antibiotics and returned to baseline visual acuity within 3 weeks. The second case was mild anterior chamber inflammation after four faricimab injections, but this was resolved with topical steroids. Notably, the same eye had had a history of anterior uveitis without occlusive vasculitis during treatment with brolucizumab.[22]

Another real-world faricimab study was done by a group in Atlanta.[23] Following the switch to faricimab, BCVA and CST improved significantly. The durability component was again apparent with the mean dosing intervals between the last two faricimab injections being significantly longer than previous intervals on ranibizumab or aflibercept.[23] In addition to our growing, collective real-world experience with faricimab, the AVONELLE-X study is an open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients who were enrolled in TENAYA and LUCERNE.[24]

PDS with ranibizumab

The PDS with ranibizumab is a sustained delivery device that is implanted in the operating room and refilled in the office every 24 weeks. It's on-label for the treatment of nAMD in individuals that have previously shown success and improvement with intravitreal anti-VEGF agents. In October 2022, the manufacturer recalled the device due to concerns that the septum had dislodged in specific cases.[25] While this is still under investigation, no new implantations are taking place; although, refills for previously implanted devices are still being continued.

The ARCHWAY trial which described the safety and efficacy of PDS in patients with nAMD, enrolled patients who had previously received at least three or more intravitreal anti-VEGF injections.[26] Patients were randomized 3:2 to receive either the PDS with a refill every 24 weeks in the office or monthly ranibizumab injections. At the primary endpoint, there was noninferiority and equivalency of visual acuity between both groups, and very similar central point thickness (CPT) on OCT.[26] Over 96 weeks, these trends were maintained.[27] Interestingly, nearly 95% of patients did not require supplemental anti-VEGF therapy over the entire 2-year period, ie, they were able to extend the full 24 weeks, only requiring the prespecified refill of the device.[27] What's more, patients liked the device.[28] By week 40, 93.2% of patients preferred the PDS to intravitreal injections. This preference is, of course, a positive because it's central to success with therapy and adherence to therapy.

"During weeks 4, 8, and 12, those treated with faricimab had a greater reduction in central subfield thickness (CST) on OCT and slightly improved visual acuity compared to those treated with aflibercept."

– Jessica Steen, OD

However, as a surgical procedure, the PDS did have significant device-related adverse events including vitreous hemorrhage, hyphema, and retinal detachment.[26] As an optometrist, what's most important to me when monitoring these patients in between visits with the retina specialist is the conjunctiva. I look for early conjunctival erosion or retraction because we know that this has been tied to an increased risk of endophthalmitis. Dr. Goldberg, can you walk us through the refill procedure?

Dr. Goldberg: It's quite straightforward; although, it is a little bit more involved than the typical intravitreal injection. We have to approach the PDS septum with the needle perfectly perpendicular to the center point of the septum. When the manufacturer investigated some of these cases of septum dislodgement, it was because practitioners had taken an inaccurate approach. Overall, while it's not quite as trivial as an intravitreal injection, the technique can be easily learned. I commend the manufacturer for being responsible with the voluntary recall and pausing the implantations. We know the PDS works, we've got great data to support that. I'm hopeful they will be able to optimize the device it to make sure that it's safe over the long-term and over several refills.

Dr. Steen: The PORTAL extension study, which included patients from the phase 2 LADDER and phase 3 ARCHWAY trials, has shown that for 4 years, mean BCVA was stable at 20/40 and mean CPT on OCT was also maintained.[29] The majority of patients were, once again, able to make it the full 24 weeks between refills without requiring supplemental anti-VEGF injections. This is very encouraging data. The safety profile was similar to what was seen in ARCHWAY, with no new safety signals.[29]

The global 5-year, real-world VOYAGER study is a massive project designed to evaluate what happens in real life with the faricimab and PDS therapies, looking at challenges with adherence, and overall safety and efficacy outcomes.[30] This study is still in the early phase, but we will eventually have a lot of high-quality data about both these therapies that will be applicable to real-world clinical practice.

Brolucizumab

The final relatively new agent that retina specialists have access to in the United States is brolucizumab. It was evaluated in the phase 3 HAWK and HARRIER trials.[31] Patients were randomized to receive either aflibercept (on-label dosing—three monthly loading doses followed by 8-week intervals) or brolucizumab, which also had three monthly loading doses followed by disease activity assessment visits which dictated the treatment interval. The maximum interval was 12 weeks. Again, because of the trial design, the first 8 to 12 weeks of treatment were a matched, direct comparison between brolucizumab and aflibercept.

Overall, brolucizumab met its primary endpoint of noninferiority in mean change in BCVA from baseline against aflibercept at 48 weeks.[31] The key feature here is durability. More than 50% of brolucizumab-treated patients in both HAWK and HARRIER were able to maintain 12-week intervals through the 48-week endpoint. By week 92, 45.4% and 38.6% of patients in HAWK and HARRIER, respectively, were maintaining a q12w regimen and brolucizumab appeared to demonstrate greater fluid resolution than aflibercept.[32] What's limited brolucizumab use in widespread clinical practice is the safety signal related to intraocular inflammation that was not seen to the same extent in patients receiving aflibercept. An independent safety review committee analyzed the investigator-reported cases of intraocular inflammation in the phase 3 trials.[33] They found that the rate of intraocular inflammation was 4.6%, with 3.3% of cases being retinal vasculitis, and 2.1% of cases being occlusive retinal vasculitis. Finally, there is a small but noteworthy incidence of 0.74% of at least moderate visual acuity loss in the eyes with occlusive vasculitis. Conversely, the rate of intraocular inflammation in the aflibercept-treated eyes was 1.1%.[33]

Looking through the IRIS registry at the real-world outcomes of treatment-experienced patients with nAMD who received only brolucizumab for at least 12 months, up to 55.4% were able to be extended by 4 weeks or greater after the switch.[34,35] In fact, 29.5% of eyes had a preswitch interval of at least 8 weeks, which increased to 83.1% following the switch to brolucizumab. More than 86% of eyes have stable or improved visual acuity at 12 months.[34,35]

The phase 3b, 64-week TALON study compared brolucizumab and aflibercept but asked whether brolucizumab was superior to aflibercept in extending the duration of treatment interval when using a matched TAE regimen in treatment-naïve patients with nAMD.[36] They tried to replicate what retina specialists would do in routine clinical practice. Notably, extending the duration means nothing if the visual acuity gains are not similar, so, noninferior BCVA gains were required. Brolucizumab was found to be superior in extending the treatment interval compared to aflibercept. The 32-week interim data showed that 38.5% of patients who received brolucizumab and 19.8% of patients receiving aflibercept were able to be maintained at 12-week intervals with zero disease activity. It is worth highlighting that the absence of disease activity in this study was defined as no intraretinal or subretinal fluid in the central macular subfield. This tolerance can vary between trials and certainly between individual clinical practice.[36]

A Swiss group has developed an almost algorithmic approach to patient selection and management of intraocular inflammatory

events in individuals undergoing brolucizumab treatment.[37] What it comes down to is early recognition and aggressive anti-inflammatory treatment to optimize long-term outcomes.[37]

In 2021 and 2022, we saw the introduction of two FDA-approved ranibizumab biosimilars.[38-40] Aflibercept biosimilars are currently in the pipeline.[41] While biosimilars are not advancing the field in terms of treatment durability, I'm curious to see what role they will play in advancing the management of patients with nAMD.

THE NEXT WAVE OF nAMD TREATMENTS AND INNOVATIONS IN DISEASE MONITORING

Dr. Goldberg: When we consider emerging therapies in the field of nAMD, we are looking at high-dose aflibercept, gene therapies, and tyrosine kinase inhibitors that may further extend durability in the way that faricimab, the PDS, and brolucizumab have pushed the field. We're also investigating enhanced efficacy—can we obtain better functional and/or anatomic outcomes with a novel VEGF-C and -D inhibitor, sozinibercept, in combination with ranibizumab or aflibercept? Finally, we're excited about remote monitoring of patients so that we can catch conversion to nAMD earlier, as well as see the granular changes in retinal fluid between injections to personalize treatment regimens.

Extending durability

High-dose aflibercept is four times the original FDA-approved dose of aflibercept 2 mg, ie, 8 mg. By quadrupling the dose, we know that we are adding two half-lives to the drug, and probably having an even longer clinical effect beyond the pure pharmacokinetics. In the phase 3 PULSAR trial, patients were randomized a priori to a 12- or 16-week regimen of 8 mg aflibercept after three monthly loading doses.[42] At weeks 16 and 20, patients meeting the dose regimen modification criteria (both vision and anatomy) could have their treatment interval shortened to 8-week dosing or continue 12- and 16-week dosing, respectively. At week 24, patients could have their interval shortened to 12-week dosing or continue on 16-week dosing.

At week 48, high-dose aflibercept was noninferior in terms of visual acuity and central retinal thickness to aflibercept 2 mg dosed every 8 weeks.[42] Additionally, a significant proportion of patients were able to maintain 12- (79%) and 16-week (77%) intervals. Overall, 83% of patients had intervals of 12 weeks or higher on high-dose aflibercept.[42] We can see that increasing the dose means that the drug is retained longer in the vitreous, leading to some extended durability. The 2-year data showed that 78% of all patients receiving high-dose aflibercept maintained intervals of 12 weeks of greater.[43] Of the patients who had been assigned a 16-week interval at baseline, 70% maintained it during the entire 2-year period. Interestingly, 71% of all patients met the criteria for even longer interval extensions—28% had 24-week intervals and 47% had intervals of 20 weeks or greater. The safety of high-dose aflibercept was similar to aflibercept 2 mg, with no new safety signals.[42,43]

In June 2023, the FDA issued a complete response letter for high-dose aflibercept due to an ongoing review of inspection findings at a third-party filler.[44] Importantly, there were no identified issues with the efficacy or safety of 8 mg aflibercept.[44] In August 2023, the drug received FDA approval for the treatment of both nAMD and diabetic macular edema, becoming the first therapy to be dosed at 8-week and up to 16-week intervals following three monthly loading doses.[45]

Gene therapy programs are the holy grail of sustained delivery of therapies. Currently, there are two programs in development–one for ABBV-RGX-314 and another for ADVM-022. Both are adeno-associated viral (AAV) vectors that contain DNA to produce ranibizumab-like or aflibercept-like protein fragments, respectively. ABBV-RGX-314 is being evaluated as a subretinal and suprachoroidal injection. The subretinal route requires a vitrectomy and creation of a subretinal bleb with a 41-gauge cannula. The suprachoroidal route uses an injector similar to that used for the triamcinolone acetonide injectable suspension, which is indicated for the treatment of macular edema associated with uveitis. ADVM-022, on the other hand, is delivered as an intravitreal injection, which will be more familiar to retina specialists. Both ABBV-RGX-314 and ADVM-022 are in earlier stage clinical trials than high-dose aflibercept, but early indications are that both treatments provide a substantial reduction in annualized injection rate for the majority of patients after a one-time injection. While there are certainly some safety issues to consider and optimize for both agents, gene therapies could lead to meaningful reductions in the anti-VEGF treatment burden.

Enhancing efficacy

Sozinibercept (OPT-302), a fusion protein similar to aflibercept, is a VEGF-C and -D inhibitor that is currently in phase 3 clinical trials. Our current cadre of anti-VEGF agents target primarily the VEGF-A isoform, but VEGF-C and -D also facilitate angiogenesis and vascular leakage, independent of VEGF-A. As Dr. Dunbar commented, there is data to suggest that the anti-VEGF effect can diminish over time. One of the reasons is that there may be other "escape routes" or mechanistic disease redundancies that cause this. We know that blocking VEGF-A leads to upregulation of VEGF-C and -D, so perhaps a combination approach might be able to improve outcomes over time.

In the phase 3 SHORE and COAST trials, which are currently recruiting, sozinibercept is being evaluated in combination with ranibizumab and aflibercept, respectively, against ranibizumab or aflibercept monotherapy, respectively. In the phase 2b trial in nAMD, combination therapy with ranibizumab showed, for the first time, superiority in visual outcomes over ranibizumab monotherapy, ie, 14.2-letter versus 10.8-letter gain from baseline, respectively.[46] We also saw that a higher proportion of patients gained more than 15 letters with combination therapy (45%) compared to ranibizumab monotherapy (40%). Even more importantly, there was a greater reduction in the proportion of patients losing more than 15 letters (0.8% vs 3.4%).[46] We don't think of this metric much anymore, but it harkens back to the days of the ANCHOR and MARINA trials where our expectation was that patients with nAMD would lose vision over time. The 2-mg dose

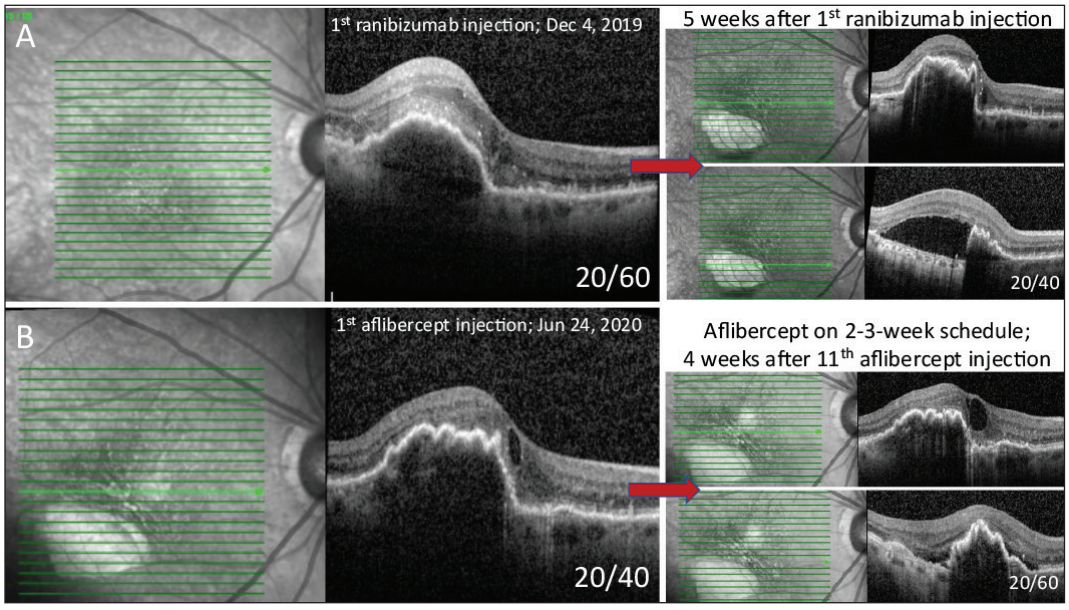

Figure 2. Patient with new-onset nAMD in the right eye (A) who developed an RPE tear after a single ranibizumab injection, which eventually resolved. (B) After receiving six additional ranibizumab injections, the patient was switched to aflibercept and maintained a strict 2-3-week interval between injections, for nearly 2 years. Courtesy of Roger A. Goldberg, MD, MBA.

of sozinibercept was taken forward to phase 3 trials and we look forward to hearing about those results in time.

Personalized medicine in retina

Currently, we have the ForeseeHome monitoring program which is a home-based device that uses preferential hyperacuity perimetry to identify visual distortions that may signal the conversion from intermediate AMD to nAMD. The original HOME study led to the approval of this device in 2009 and a recent real-world study showed that the system performed similarly in the real world as the pivotal trial.[47,48]

Recently, results from the 10-year ALOFT study, which is a large, retrospective study involving more than 2,000 patients, were published.[49] It showed that patients were testing their vision at home with the device an average of 5.2 times a week during the 10-year period. The most important finding in the study was that patient VA at conversion was 20/39 when they used the device versus 20/83 when patients were using "the standard of care," which is an Amsler grid and likely a follow-up every 6 months or so.[13,49] One of the best predictors of visual acuity outcomes at 1 or 2 years after initiating treatment, is of course, visual acuity at the time of diagnosis. The ALOFT study showed that the ForeseeHome device can substantially improve baseline visual acuity and hopefully, start our patients off on the right foot. Indeed, more than 80% of patients, whose conversion was detected using the device, were able to maintain functional vision (20/40 or better).[49]

Another home monitoring device is the Home OCT, which is a home-based OCT unit that a patient with nAMD self-operates. It is connected to a cloud-based AI software that helps to monitor disease progression in the retina. Early studies have shown the system can successfully be used to generate eligible scans by the majority of patients more than 90% of the time.[50,51] What's exciting about this device is that we can monitor changes in retinal fluid volume over time, so that we're using patient anatomy rather than symptoms to guide our clinical decision-making. The hope is that this technology can help reduce the number of times patients need to visit our offices as well as address the issue of patient undertreatment.

CASE 1: IMPROVED ANATOMIC AND DURABILITY OUTCOMES WITH SECOND-GENERATION ANTI-VEGF AGENTS

Dr. Goldberg: This was a patient of mine, an 83-year-old pseudophakic White male, first diagnosed in our clinic with intermediate AMD. In June 2018, he had 20/40 VA in both eyes, diffuse drusen, some reticular pseudodrusen, but no evidence of nAMD, so he was sent back to his referring optometrist. He returned to me in December 2019 when he developed nAMD (Figure 2A). His VA was 20/60 in the right eye and I treated him with a ranibizumab injection at this time. He returned 5 weeks later with slightly better VA, ie, 20/40; however, he had now developed an RPE tear, which you can see nicely on the OCT and the infrared image on the left. Thankfully, though, the fovea was still covered by RPE.

I continued to treat him with ranibizumab during the next few months. After the sixth ranibizumab injection in June 2020, I switched him to aflibercept (Figure 2B). He was doing well initially but started to require aflibercept injections at 2- to 3-week intervals to keep from developing intraretinal fluid. In September 2021, 4 weeks after the 11th aflibercept injection, he had both intraretinal and subretinal fluid, and VA was 20/60. A few months later in January 2022, faricimab was approved for the treatment of nAMD, so 4 weeks after he received his 20th aflibercept injection, I gave the patient a faricimab injection in April 2022 (Figure 3A). A month later, you can see significant improvement not just in the vision (20/60 to 20/40), but also in the anatomy, with that intraretinal fluid starting to resolve (Figure 3B). Unfortunately, the patient didn't have authorization from their insurance provider for faricimab, so I had to switch him back to aflibercept. Four weeks later, he returns and not surprisingly, has gotten worse, with VA dropping to 20/50 and significant reaccumulation of fluid (Figure 3C). Thankfully by then, I'm able to return him to treatment with faricimab, initially extending to a 6-week interval (Figure 3D) and eventually to an 8-week interval. He's still on faricimab now and on a 7- to 8-week interval.

This was a nice example of a patient going through a range of anti-VEGF agents during the past few years and demonstrating each time why he had to, especially when he clearly did worse on that brief switch from faricimab back to aflibercept.

Dr. Dunbar: Is that because faricimab was not first-line according to the insurance provider and so they required the patient to "fail" on one of the other first-generation anti-VEGF agents before authorizing faricimab?

Dr. Goldberg: It really depends on the patient's insurance. Every insurance is different. Thankfully, we have an entire team at the practice who deals with revenue cycle and authorization, because otherwise, it's very confusing. In California, where I practice, it's a highly managed state. Oftentimes, we do have to step through one or two therapies. Faricimab has been on the market for more than a year now and thankfully, it's now available to more than 80% of covered lives, sometimes after a trial of at least one bevacizumab injection.

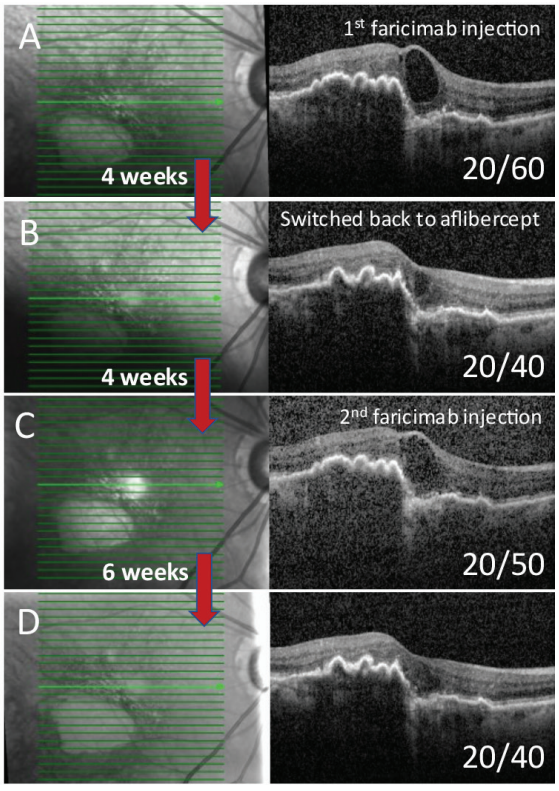

Figure 3. Patient with nAMD in the right eye who received alternating faricimab and aflibercept injections due to initial insurance authorization issues. Courtesy of Roger A. Goldberg, MD, MBA.

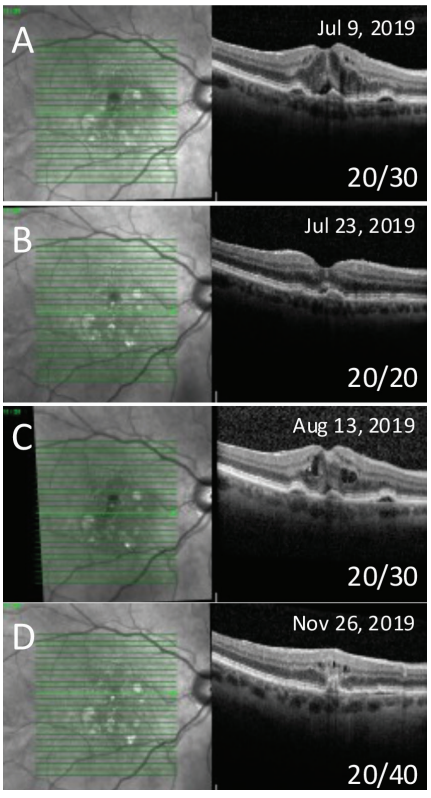

Figure 4. Patient with nAMD with (A) who had received three bevacizumab and two aflibercept injections before being given a third aflibercept injection. (B) Two weeks later, anti-VEGF responsiveness was confirmed and (C) the patient remained on monthly aflibercept receiving seven injections total. (D) When brolucizumab became available, the patient received a single dose. Courtesy of Roger A. Goldberg, MD, MBA.

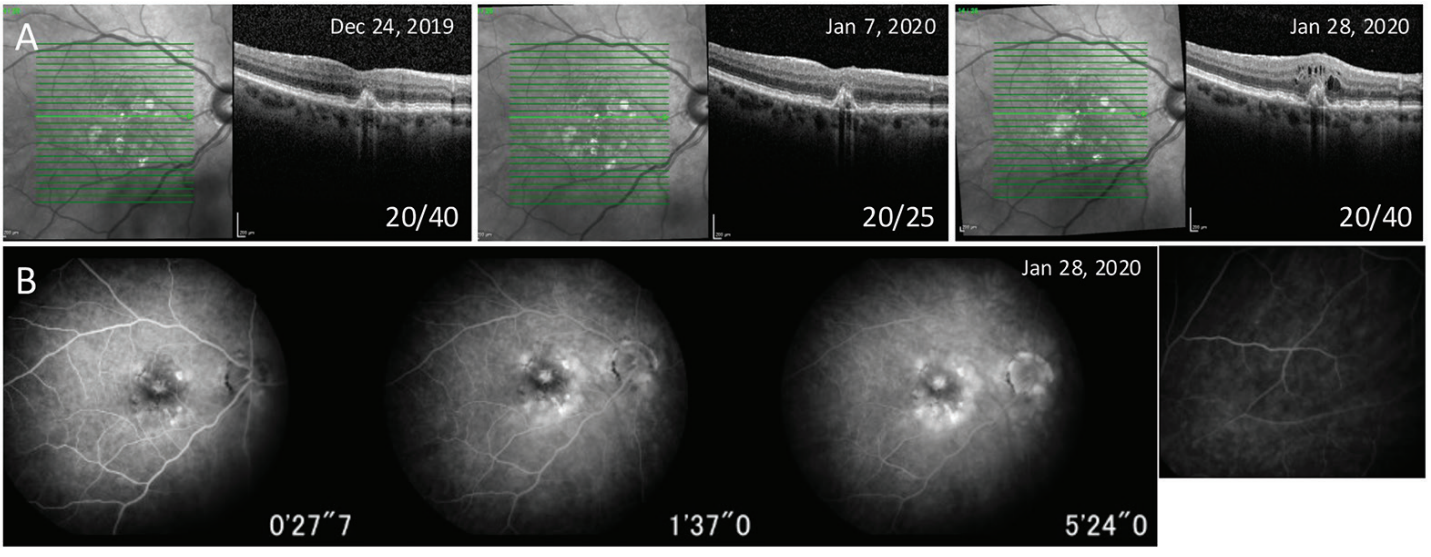

Figure 5. Patient with nAMD who (A) complained of floaters and blurred vision 4 weeks after a single brolucizumab injection and was treated with topical steroids. Two weeks later, vision had returned to baseline, anterior chamber cells had resolved, topical steroids were tapered, and the retina remained dry for a further 3 weeks. (B) After confirming that the patient had no signs of occlusive vasculitis, they were switched back to aflibercept injections. Courtesy of Roger A. Goldberg, MD, MBA.

CASE 2: ONCE BITTEN, TWICE SHY

Dr. Goldberg: Our second case is a pseudophakic, 72-year-old White female who was diagnosed with nAMD in the right eye in January 2019, with 20/40 VA. She had previously received three bevacizumab and two aflibercept injections. In July 2019, 5 weeks after a second aflibercept injection was given, I gave her a third injection (Figure 4A). She came back 2 weeks later because I wanted to confirm anti-VEGF responsiveness and make sure I had the right diagnosis. She looked great and VA improved to 20/20 (Figure 4B). In August 2019, just 5 weeks after the third aflibercept injection, VA dropped to 20/30, fluid worsened, and the patient became much more symptomatic (Figure 4C). I continued her on monthly aflibercept injections until brolucizumab became available, at the time. In November 2019, 4 weeks after the seventh aflibercept injection, I administered the first brolucizumab injection (Figure 4D).

I saw her again 4 weeks later and she was complaining about floaters and blurred vision since the last injection, despite this great-looking anatomy on the OCT (Figure 5A). The conjunctiva was white and quiet, but I looked in the anterior chamber and saw 10 cells per high-powered field, but thankfully, no flare or fibrin. There was no anterior or posterior evidence of inflammation, specifically none of the occlusive vasculitis that we now worry so much about.

I treated her with qid topical prednisolone and, fortunately, she did well. By January 2020, she had returned to baseline, anterior chamber cells had resolved, and the topical steroids were tapered. This was 6 weeks after the first brolucizumab injection and she was still dry. This was a patient I couldn't get dry on monthly aflibercept but was now dry with brolucizumab. It wasn't until 9 weeks after the first brolucizumab injection that the fluid returned. Of course, because this patient had already had inflammation with brolucizumab, I did not retreat her with another dose. This was much to her chagrin because she was so happy to have gone 2 months between injections, instead of 1, but I did not want to risk rechallenging this patient with brolucizumab. So, I switched her back to aflibercept. Figure 5B shows there in no evidence of significant vasculitis.

With that, I'd like to thank Drs. Dunbar and Steen for their participation in this program. It's been phenomenal, really rich in material and insights. ■

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nAMD Collaborative Care: Current Challenges and Potential Solutions

COPE Release Date: September 26, 2023
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INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached **Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form** and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, go to https://evolvemeded.com/course/2324-supp-1. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

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

Full Name_____ DOB (MM/DD): _____

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Address/P.O. Box_____

City _____ State/Country _____ Zip _____

License Number:_____OE Tracker Number:_____National Provider ID:_____

*Evolve does not share email addresses with third parties.

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
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 neovascular age-related macular degeneration (nAMD) (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 how often you will be able to resolve barriers to optimal treatment outcomes for patients with nAMD (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 about the number of anti-VEGF injections and vision outcomes in nAMD is TRUE?

A. Higher number of anti-VEGF injections correlates with better vision outcomes in nAMD
B. Higher number of anti-VEGF injections correlates with worse vision outcomes in nAMD
C. The number of anti-VEGF injections does not correlate with vision outcomes in nAMD
D. The number of anti-VEGF injections correlates with vision outcomes only in vision that is > 20/40 at diagnosis

4. You are evaluating an 88-year-old patient with nAMD. His OCT shows cystic intraretinal fluid overlying a fibrovascular pigment epithelial detachment. He lives more than 75 miles away from the nearest retina practice and has limited mobility. Which of the following options represents the best therapeutic option for this patient?

A. Intravitreal bevacizumab monthly
B. Intravitreal ranibizumab monthly
C. Intravitreal corticosteroid therapy
D. Longer acting therapy such as faricimab or port delivery system with ranibizumab

5. Which of the following characteristic of patients with nAMD receiving anti-VEGF therapy increases risk of being lost to follow-up?

A. Caucasian race
B. Young age (50-60)
C. Medicaid insurance
D. Medicare fee-for-service insurance

6. You are evaluating a 78-year-old patient with newly diagnosed nAMD. She is well versed in the current clinical trials and is excited about starting anti-VEGF therapy for her condition. She asks if she can expect a similar number of yearly injections as noted in the trials. What is the best response for this patient?

A. Real-world patients with nAMD receive fewer injections than patients in clinical trials
B. Real-world patients with nAMD receive more injections than patients in clinical trials
C. Real-world patients with nAMD receive equal injections to patients in clinical trials
D. Real-world patients > 70 years old with nAMD receive more injections than patients in clinical trials

7. According to the literature, real-world injection data indicate that patients with nAMD received _____ injections per year:

A. 3 to 4.5
B. 4 to 5.7
C. 6 to 7.6
D. 9 to 10.5

8. You are evaluating a 67-year-old male with nAMD on monthly ranibizumab. He is well controlled on this medication with a dry OCT; however, he cannot be extended beyond 4 weeks. He has previously failed both aflibercept and faricimab. He finds his monthly injections burdensome and wishes for a more durable option. Which is the most reasonable option for this patient?

A. Switch to monthly aflibercept
B. Switch to monthly bevacizumab
C. Switch to monthly faricimab
D. Consider the port delivery system with ranibizumab if available

9. What is the mechanism of action of OPT-302?

A. Blocks all VEGF isoforms
B. Blocks VEGF-A and VEGF-B
C. Blocks VEGF-C and VEGF-D
D. Block VEGF-A and VEGF-C

10. ADVM-022 is a novel therapeutic meant to deliver a gene encoding for an anti-VEGF protein into the eye. How is this medication delivered?

A. Oral pill
B. Subretinal injection
C. Intravitreal injection
D. Intramuscular injection

11. RGX-314 can be delivered into the eye by which of the following methods?

A. Subretinal injections/suprachoroidal injection
B. Intracameral injection
C. Topical suspension
D. Intravitreal injection

12. A 72-year-old woman presents to your office with a diagnosis of nAMD OD. She has a prior history of receiving bevacizumab and aflibercept and is currently on monthly aflibercept treatment. She has persistent cystic intraretinal fluid and subretinal fluid despite monthly aflibercept injections. Her retina specialist switches to brolucizumab OD. One month later, she complains of floaters and blurred vision since her last brolucizumab injection and you note 10 cells/hpf in her anterior chamber, with no other symptoms or signs. What is the next best step in management?

A. Vitreous tap and inject for presumed endophthalmitis
B. Start prednisolone drops four times daily for anterior segment inflammation
C. Start acyclovir for presumed herpetic infection
D. Start moxifloxacin drops for presumed infection

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.

_____

_____