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nAMD Management in the Real World:

Practical Tips for Treating Patients

DIANA V. DO, MD
PROGRAM CHAIR

GEETA A. LALWANI, MD

EHSAN RAHIMY, MD

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Faculty

Diana V. Do, MD
Program Chair
Vice Chair for Clinical Affairs
Professor of Ophthalmology
Byers Eye Institute
Stanford University School of Medicine
Palo Alto, CA

Geeta A. Lalwani, MD
Vitreoretinal Surgeon
Rocky Mountain Retina Associates
Boulder, CO

Ehsan Rahimy, MD
Department of Ophthalmology
Palo Alto Medical Foundation
Palo Alto, CA
President and Cofounder, HealTheia

Content Source

This continuing medical education (CME) activity captures content from a live-virtual symposium.

Activity Description

This supplement summarizes a discussion on current treatments for neovascular age-related macular degeneration (nAMD) and how pipeline therapies may result in better outcomes for patients.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Describe** the current treatments available to treat neovascular age-related macular degeneration (nAMD)
- **Discuss** the considerations involved in the choice of anti-VEGF agent and tailoring treatment regimens for individual patients
- **Evaluate** clinical evidence for biomarkers that are prognostic of optimal visual outcomes
- **Summarize** the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in nAMD

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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 summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in 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. According to treat-and-extend trials of anti-VEGF dosing for nAMD, what percentage of patients were able to achieve treatment intervals of at least 12 weeks?

A. ~20%
B. ~30%
C. ~40%
D. >50%

3. A 68-year-old patient presents to your clinic for initial evaluation. She has a history of recurrent anterior iridocyclitis and AMD. She notes recent onset of blurry vision in her right eye. On examination you note a normal exam except for subretinal hemorrhage OD and her OCT has evidence of new cystic intraretinal fluid. What is the next appropriate step in management of this patient?

A. Observation
B. Initiate topical prednisolone four times a day
C. Initiate intravitreal aflibercept treatment
D. Initiate intravitreal steroid treatment

4. A 68-year-old patient with nAMD presents to your clinic for follow-up. She has had improvement in both BCVA and OCT anatomy on monthly aflibercept; however, she still has intraretinal fluid present in her macula. You discuss switching to faricimab with this patient. All of the following statements about faricimab are true EXCEPT:

A. Studies have shown a decrease in central subfield thickness (CST) after switching to faricimab
B. Studies have shown an increase in CST after switching to faricimab
C. Studies have shown significantly longer mean dosing intervals with faricimab than ranibizumab or aflibercept
D. Studies have shown improved BCVA after switching to faricimab

5. An 86-year-old White man presents to your office for evaluation. You diagnose him with nAMD and recommend he start monthly anti-VEGF treatment. He has Medicaid insurance and is worried about his ability to pay for treatments and about the pain of injections. All of the following include risk factors for loss to follow-up for this patient EXCEPT:

A. Age
B. White race
C. Medicaid insurance
D. Fear of injections

6. You are evaluating a 75-year-old patient with nAMD. She has experienced recurrent intraretinal fluid despite monthly ranibizumab as well as aflibercept. She has a history of recurrent intraocular inflammation. What is the next most reasonable treatment option?

A. Switch to brolucizumab
B. Switch to faricimab
C. Inject intravitreal corticosteroids
D. Perform photodynamic therapy

nAMD Management in the Real World: Practical Tips for Treating Patients

Although anti-VEGF injections are safe and effective treatments for patients with retinal diseases such as neovascular age-related macular degeneration (nAMD), real-world outcomes rarely align with the successes seen in clinical trials. Patients require chronic, frequent injections to optimize visual outcomes; however, the burden of frequent office visits is challenging for patients and their caretakers. Missed visits lead to undertreatment and disease progression leading to suboptimal visual acuity outcomes and negative effects on quality of life. As such, retinal specialists and patients seek new medicines with longer duration of disease control and longer injection intervals. The following panel discussion reviews the considerations involved in the choice of anti-VEGF agents and how to tailor treatment algorithms for individual patients. We'll also evaluate clinical evidence for biomarkers that are prognostic of optimal visual outcomes and summarize the advances in VEGF inhibition that may improve treatment outcomes or reduce treatment burden in patients with nAMD.

— Diana V. Do, MD, Program Chair

NOTE: *This panel discussion occurred prior to the approval of 8-mg aflibercept.*

TREAT AND EXTEND: BALANCING INJECTION BURDEN AND VISUAL OUTCOMES

Geeta A. Lalwani, MD: We are all aware of the significant burden of AMD in the United States; both in terms of vision loss as well as the treatment burden that results in retina clinics full of patients. What is remarkable is that of the more than 18 million patients who have AMD, only 10% have late-stage disease, which is either nAMD or geographic atrophy (GA).[1] Only a small percentage of these 18 million patients have nAMD and are currently in our retina clinics.

Anti-VEGF treatments for AMD have evolved over the years. Early anti-VEGF treatments recommended a monthly fixed-dose regimen. Based on some early small clinical trials such as PrONTO, we have tried to determine the right interval that balances outcomes and injection burden, such as fixed quarterly regimen, pro re nata, or treat and extend (T&E).[2-7]

ALTAIR and ARIES are two trials that assessed T&E as a dosing regimen.[8-11] ALTAIR evaluated efficacy and safety of aflibercept T&E dosing regimens in treatment-naive patients with nAMD. Patients received three monthly doses of 2-mg aflibercept. At week 16, patients were randomly assigned 1:1 to aflibercept T&E with either 2- or 4-week adjustments. The primary endpoint was mean change in best-corrected visual acuity (BCVA) from baseline to week 52, with outcomes assessed at weeks 52 and 96.[9]

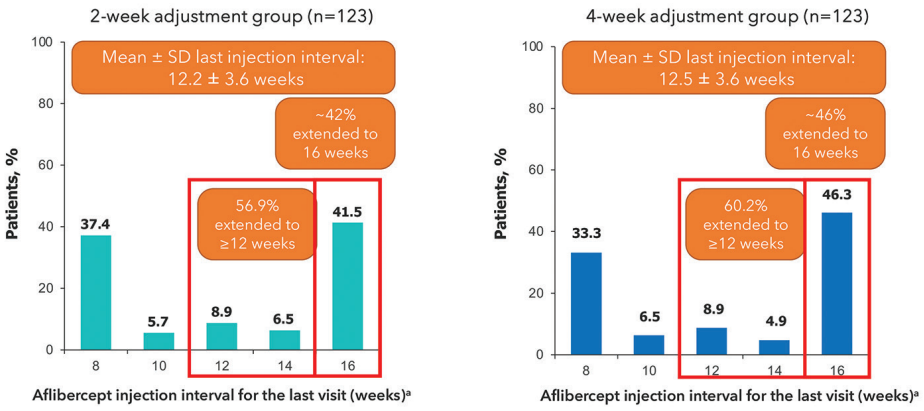
ARIES also evaluated the efficacy and safety of T&E dosing with aflibercept in treatment-naive patients with wet AMD, but in two different arms. In one arm, patients received a fixed-dosing interval for the first year and then entered into a T&E regimen. This was termed late-start T&E versus early-start T&E patients who entered into T&E from the very beginning.[10] Patients received 2-mg aflibercept at weeks 0, 4, 8, and 16, when they were randomly assigned 1:1 to early-start (2-week interval adjustments) or late-start T&E (8-week intervals until week 48, then 2-week interval adjustments). The primary endpoint was BCVA change from random assignment to week 104.

These trials are similar in that they're trying to mimic what we do in clinical practice, but they do differ slightly. ARIES was conducted across eight countries, whereas ALTAIR was conducted in Japan. For extension criteria, ARIES tolerated a small amount of subretinal fluid, less than 50 µm, versus ALTAIR, which did not tolerate any fluid for extension. However, ALTAIR did tolerate a small amount of residual fluid to maintain the dosing interval. Both of the criteria in which investigators shortened the interval were similar and included an increase in fluid, a drop in vision, or the presence of a hemorrhage.

In ALTAIR, at 96 weeks, the vast majority of patients had extended to 12 weeks and beyond (Figure 1). In ARIES, the two arms had similar outcomes, with 48% to 52% able to extend beyond 12 weeks. The majority of those patients were able to extend to 16 weeks and beyond (Figure 2).

When we looked at the ARIES post-hoc analysis, we found that the outcomes were very similar between the groups.[12] Irrespective of an early or late start, there was only a one injection difference over 2 years, which tell us that most patients in the early T&E group needed a more frequent injection in the beginning. Still, almost a quarter of patients had a single treatment interval of less than 8 weeks. Mean treatment-interval was 8.4 weeks before and 6.1 weeks after determining an injection-intensive treatment was required. Nearly 60% of all injection-intensive patients achieved treatment intervals of ≥ 8 weeks following injection-intensive determination.

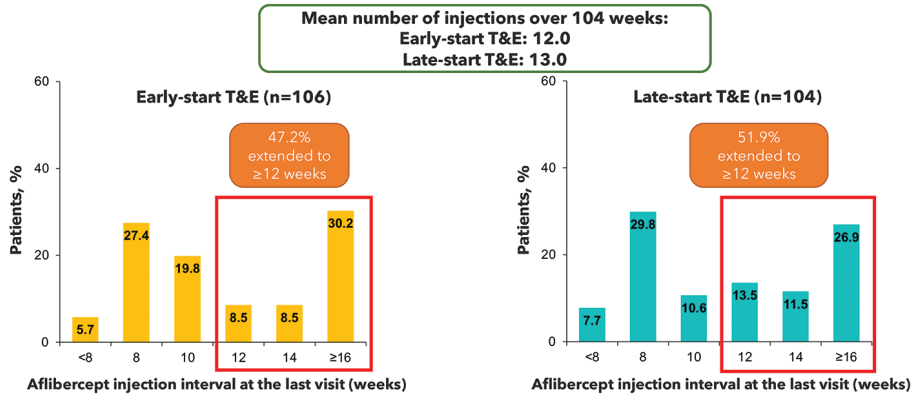
In ALTAIR, there was a subpopulation of 90 patients with treatment-naive polypoidal choroidal vasculopathy.[13] They underwent two different regimens of either 2- or 4- week adjustments. Following three initial monthly doses of aflibercept, at week 16 patients were randomly assigned to T&E regimens with either 2- or 4-week adjustments. From baseline to week 96, 91.3% and 90.9% of patients maintained vision in the 2- and 4-week groups, respectively. From baseline to week 52, mean change in central retinal thickness (CRT) was − 153 (177) µm and −112 (122) µm in



Full analysis set. a The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks.

Adapted from Ohji M, et al. Presented at: The 18th European Society of Retina Specialists (EURETINA) 2018 Congress; September 20-23, 2018; Vienna, Austria.
Ohji M, et al. Adv Ther. 2020;37(3):1173-1187. Open access under a Creative Commons NC license.

Figure 1. ALTAIR week 96 results.[9]



Not all use of aflibercept in this clinical trial was in accordance with the licensed posology. Please see the aflibercept summary of product characteristics for details of the licensed posology. Analyses were conducted as a last observation carried forward from the per-protocol set. Intervals greater than 16 weeks were considered minor deviations and were included in the PPS.

Adapted from Mitchell P, et al. Retina. 2021;41(9):1911-1920.

Figure 2. ARIES week 104 results.[10]

the 2- and 4-week groups, respectively. Overall, 51% of patients achieved a treatment interval of 16 weeks between weeks 16 and 96.

The safety profile of aflibercept was consistent with previous large aflibercept studies. Dr. Do and Dr. Rahimy, how do you manage fluid and determine which patients to extend and which to maintain?

Ehsan Rahimy, MD: As with many things in our field, there's no clear-cut answer. Ideally, we don't tolerate intraretinal fluid, but may have a bit more leniency with subretinal fluid.[14-16] We each have certain patients whom we get as dry as possible, yet they may still have a small amount of residual subretinal fluid. Then you're then faced with a decision: do you keep that patient on frequent treatment every 4-or-so weeks and maintain a high injection burden, or do you still try to gradually space them out over time provided the amount of exudation stays minimal and stable? In those situations, I've found that, more often than not, I'm able to slowly extend patients out further as long as I'm not seeing an increase in the exudative disease process and their vision remain stable.

Diana V. Do, MD: I agree that we try to eliminate any sign of disease activity. Our approach is individualized to each patient, and retrospective studies have shown that tolerating small amounts of persistent subretinal fluid may not always be deleterious to the vision. Many retinal specialists will switch anti-VEGF agents to try to eliminate that residual fluid. Now that we have even more treatment options available, I think trying new anti-VEGF agents becomes more attractive to both the patient and the physician.

REAL-WORLD VERSUS CLINICAL TRIAL OUTCOMES IN nAMD

Dr. Do: Dr. Lalwani gave us some excellent data from the ARIES and ALTAIR studies, but do we achieve these visual acuity outcomes in our clinical practice? A retrospective study from Ciulla et al assessed anti-VEGF therapy intensity and its relationship with visual acuity change in treatment-naive, real-world patients with nAMD (N = 49,485 eyes) between January 2012 and October 2016.[17] Real-world patients with nAMD received fewer injections than patients in clinical trials (7 vs 8 to 12 injections) in the first year.[18,19] How did the reduction of anti-VEGF injections in the real world affect vision? The Ciulla et al paper found that vision outcomes correlated with the number of injections received.[17]

Patients who had more injections (9 to 10+ a year) had improved visual acuity. If you received 6 or fewer injections over a 1-year period, vision didn't improve. In fact, if you received 4 or fewer injections, you were more likely to lose vision. Therefore, with our current VEGF inhibitors, more injections will provide patients with a better chance of vision gain.

Why is it that in clinical practice, patients don't receive as many treatments as they do on clinical trials? First, there may be a lack of knowledge about the association with increased number of injections and better vision.[20] Many of our patients are elderly and lack mobility and have difficulty with transportation. Some patients fear injections or fear receiving a poor prognosis. They often have other conditions that need medical attention, and it's hard to come back on a fixed schedule that requires frequent injections. What barriers do you all see in your practices?

Dr. Rahimy: Clinical trials take place in a vacuum, whereas patients in our clinical practices are impacted by myriad

real-world factors which may influence treatment outcomes. Our patients become sick, they are hospitalized, or may have to miss an appointment due to some other obligation that comes up, and it can be surprisingly easy for them to fall off the radar. We don't have great ways or resources to pull them back like we do in clinical trials to make sure patients adhere to the follow-up visits and treatment schedules. We also can't ignore the fact that clinical trials have stringent inclusion/exclusion criteria that many of the patients we end up treating on a day-to-day basis may not have necessarily met.

Dr. Do: Patient compliance is a complex situation. Within the elderly patient population, frequent visits are a big burden. Almost 80% of patients and their caregivers report disruptions to their routine on the day of, after, and during their anti-VEGF treatments.[21]

What about suboptimal outcomes in the real world? We said that one reason for suboptimal outcomes is fewer injections of anti-VEGF agents. CATT study data showed that 51.5% and 67.4% of patients in CATT who received monthly ranibizumab and bevacizumab, respectively, had fluid on OCT even after 2 years of treatment.[22] In VIEW1 and VIEW2, 19.7% to 36.6% of patients showed persistent fluid following 1 year of 2Q4 or 2Q8 aflibercept.[23] Dr. Lalwani, what is your definition of suboptimal response, and why and when do you switch to a different anti-VEGF agent?

Dr. Lalwani: I rank fluid presence by location. I am bothered most by intraretinal fluid, but I would consider the presence of any fluid to be a suboptimal response. A very short interval could also be considered a suboptimal response, or at least the need for us to try something different. A 4-week interval is difficult for patients to maintain and the risk of noncompliance is high.

Dr. Do: Dr. Rahimy, many of us employ step therapy. If you practice step therapy, how many injections do you typically do before advocating for a switch?

Dr. Rahimy: It's open-ended. Some of it is dictated by payers, with some mandating a certain number of injections of bevacizumab first. I've heard from some colleagues that they are encountering multiple step-ups, where after bevacizumab failure, they're being mandated to switch to a ranibizumab next. Other times the definition and number of injections is up to the physician, which I find to be more harmonious. Instead of being forced to do a set number of injections, we can switch over if the patient isn't having a great response after one injection.

Dr. Do: I agree. We need to keep these decisions in physician's hands, because we want to do what's best for our patients. Let's discuss first-generation anti-VEGF agents and step therapy. Dr. Lalwani, if you had to employ step therapy and the patient has not responded optimally, what is your next therapeutic step?

"Almost 80% of patients and their caregivers report disruptions to their routine on the day of, after, and during their anti-VEGF treatments."

– Diana V. Do, MD

Dr. Lalwani: Second moves after step therapy are often dictated by insurance and include both ranibizumab as well as aflibercept. In my insurance markets, faricimab is usually more restricted by insurance panels. Given the longevity of use, I usually move to aflibercept as my first change after bevacizumab. The fact that we actually have numerous options to switch to is a testament to how far we have come in the field of retina.

Dr. Do: Dr. Rahimy, have you used biosimilars?

Dr. Rahimy: I am hesitant to take someone who has been stable on long-term ranibizumab and switch them to a biosimilar, with which they may potentially have an adverse event however small that risk may be. We don't use biosimilars in our practice, but I know different practice environments do. I haven't heard negative things from colleagues, but it's not part of the discussion currently where I practice.

Dr. Do: How do you feel your patient outcomes compare to those in clinical trials?

Dr. Lalwani: I use a T&E approach for all patients, and I treat to dry, switching to a different anti-VEGF agent if needed. The vast majority of patients either get to a point of no fluid or as good as they can be. However, this does not necessarily mean that visual outcomes mimic those of clinical trials. Outcomes in the clinic seem to reflect the outcomes of real-world studies whose visual outcomes seem closer to what we achieve in the clinic. I have been a little surprised by how few injections patients receive in real-world studies, which makes me question their treatment strategy.

Dr. Rahimy: Retina specialists think at a high level that all of our patients are doing well until we crunch the numbers and see that maybe not everyone is doing as well as the clinical trials would suggest. There are many plausible explanations for this,

which we have discussed. Some patients may have had poorer vision at presentation due to a potential delay in seeking initial care. Therefore, their visual gains may be limited, and that can obviously drag down real-world results. That type of patient may have been excluded from being in a trial due to their vision being below the lower boundary limit (ie, 20/320).

Dr. Do: I saw a patient yesterday who I have been treating for more than 5 years. Their vision has been declining during the past year, not because there's active nAMD, but because she's developing macular atrophy from progression of the dry AMD. Published studies have shown that, despite intensive anti-VEGF therapy, progression of macular atrophy can also lead to poor vision outcomes.[24,25]

Dr. Lalwani: Clinical trials on average are 1 to 2 years. The long-term progression of dry macular degeneration is not evident in that short a time period.

RECENT ADVANCEMENTS IN nAMD TREATMENT

Dr. Rahimy: I'm going to now touch on recent approvals for nAMD. Although anti-VEGF is certainly one of the greatest advents of modern medicine, we still have a lot left to achieve. Some new treatments seemed exciting at first but have since either fallen out of favor. Our three newest available therapies to the field are brolucizumab, the port delivery system (PDS) with ranibizumab, and faricimab.[26-28]

Brolucizumab

Dr. Rahimy: Brolucizumab was evaluated against aflibercept in the clinical phase 3 trials HAWK and HARRIER.[29,30]

HAWK and HARRIER were the first clinical trials in this space to employ disease activity assessment (DAA) periods. In the match phase, patients received three loading doses of either brolucizumab or aflibercept, and then did not receive anything for 8 weeks. At week 16, they entered the DAA. There was a whole host of different criteria that was used at that time to determine if a patient would remain on 12-week dosing or be adjusted to every 8-week dosing.

Many people in our field want to cross-compare trials. Do you have any thoughts on that? Is this an important consideration?

Dr. Do: Trial comparisons are extremely challenging because they all have different criteria for when to extend or to shorten the interval for re-treatment in their protocols.

Dr. Lalwani: They also have various time points of injection. visual acuity measurements are very difficult to compare unless you know exactly when the last dose was and what the interval was prior to the last dose.

Dr. Rahimy: Those are excellent points and important for our audience to remember. We will be swamped with clinical trials moving forward. I encourage you look at the DAAs and see how they potentially mirror your practice patterns. If you compare the DAAs across studies, you'll see that they're quite different. As a result, this can make cross-trial comparisons very challenging, and I'd strongly discourage my colleagues from doing them.

"As a pooled group, 83% of high-dose aflibercept patients achieved a Q12 week or greater interval."

– Geeta A. Lalwani, MD

There was a lot of initial enthusiasm when brolucizumab was approved because it seemed to be a better drying agent and potentially could help us extend treatment intervals. However, a proportion of patients had intraocular inflammation events.[29,30] Have you treated patients with inflammation related to brolucizumab?

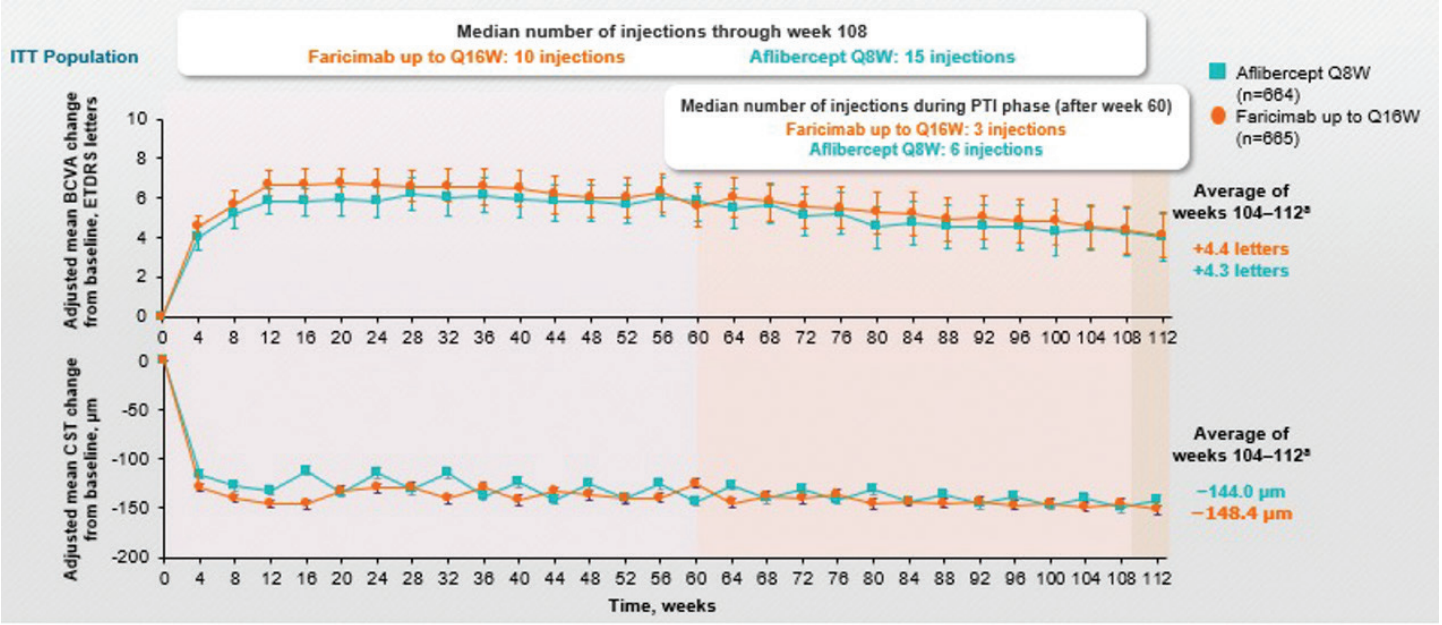
Dr. Do: One of my patients on brolucizumab developed intraocular inflammation in the form of vitritis. Luckily, it did not escalate to retinal vasculitis, but other colleagues have had patients with less fortunate outcomes.

Dr. Rahimy: Once these safety signals were identified, a retrospective cohort analysis of patients with nAMD in the IRIS registry who received brolucizumab-only treatment for at least 12 months between 2019 and 2021 was conducted to assess real-world outcomes.[31,32] On one hand, the drug worked quite well and achieved excellent anatomic outcomes. Among treatment-experienced eyes, 30% had preswitch interval at least 8 weeks versus 83% had brolucizumab interval at least 8 weeks at 12 months (mean interval of 10.3 ± 4.0 weeks). There wasn't much visual acuity benefit to a treatment-experienced population; it was about getting more durability and stretching the treatment interval. Although brolucizumab worked from that standpoint, the safety issues have severely limited its use.

Dr. Lalwani: I do not use brolucizumab due to the incidence of severe inflammation.

Dr. Do: We stopped using it because of the safety issues.

Dr. Rahimy: I have two patients in my practice who are treated with brolucizumab. They've done well with it, but it's fallen out of favor overall, and I don't find myself turning to use it for new patients.



Results are based on a mixed model for repeated measures analysis in the intention to treat (ITT) population. The median number of injections are based on the safety-evaluable population. 95% CIs are shown. CST is measured as ILM-RPE (internal limiting membrane/retinal pigment epithelium), as graded by central reading center. [a] Adjusted mean change from baseline at 2 years, averaged over weeks 104, 108, and 112. PTI dosing regimen was delayed in some patients due to dose holds or missed visits.

Figure 3. Visual acuity gains and CST reductions from baseline with faricimab.[34]

Faricimab

Dr. Rahimy: Faricimab is our first bispecific molecule, and it targets both VEGF-A and angiopoietin-2 (Ang-2). The two antigen-binding sites allow faricimab to enhance vascular stability, reduce inflammation and vascular leakage, and inhibit vascular leakage and neovascularization. The modified Fc reduces systemic exposure and inflammatory potential.

TENAYA and LUCERNE were the landmark trials that set the stage for its approval for nAMD.[28,33] Like in HAWK and HARRIER, the comparator arm was aflibercept. The DAA period was at a slightly different time point with slightly different criteria than HAWK and HARRIER, so you can only take these results in context of this trial.

In the faricimab treatment arms, patients received four loading doses. In the aflibercept arm, patients received three loading doses. Patients then went into the DAA period. Patients in the aflibercept arm stayed on an 8-week dosing regimen and were not allowed to partake in any extended interval because it was not on label. Patients in the faricimab arms could be extended into one of three arms (8,- 12,- or 16-week intervals) based on their DAA criteria. Patients remained in that swim lane for the duration of year 1. In year 2, patients were moved to what the investigators called a personalized treatment interval (PTI), which is meant to emulate as close to what we do with T&E as is possible in a registrational trial setting. The primary endpoint was mean change from baseline in BCVA averaged over the week 40, 44, and 48 visits. Both agents had similar results, with a robust rise in visual acuity that's maintained throughout years 1 and 2 (Figure 3).

TRUCKEE was a real-world, 6-month safety and efficacy analysis of faricimab in nearly 400 patients.[35] After three faricimab injections, mean BCVA improved in previously-treated (+2.7 letters, $P = .045$) and treatment-naive (+8.1 letters, $P = .437$) eyes. Mean CST decreased in previously-treated (-38.1 µm, $P < .001$) and treatment-naive (-80.1 µm, $P < .204$) eyes. There was a reduction in the number or the proportion of patients who had persistent intraretinal fluid, subretinal fluid, and PEDs. I'd consider the modest visual acuity improvement negligible since this is a mostly treatment-experienced population undergoing the switch.

In another real-world analysis, Georgia Retina conduced a retrospective review of patients receiving at least three faricimab injections with at least 3 months of follow-up (N = 190 eyes).[36] Prior to faricimab, patients had a mean 34.2 ± 23 anti-VEGF injections over 182.41 ± 128 weeks. After switching to faricimab, patients improved to a mean 6.99 ± 2.3 faricimab injections with average 34.88 ± 8.2 weeks of follow-up. BCVA improved from ~20/43 to ~20/37, which I consider modest. They had a pronounced CST reduction, improving from 312 ± 87 µm to 287 ± 71 µm, with a greater proportion of patients with no subretinal or intraretinal fluid at last clinical visit.

PDS With Ranibizumab

Dr. Rahimy: The PDS with ranibizumab was approved in October 2021 for the management of nAMD in eyes with at least two prior anti-VEGF injections.[27] This is a paradigm-shifting surgical procedure to implant a device that releases concentrated ranibizumab into the eye.[37] In October 2022, the manufacturer

announced a recall due to reports of septum dislodgement.[38] Implantations have been paused, but refills continue. I have not used the PDS personally. Do either of you have experience with it?

Dr. Do: We were involved in the early-phase clinical trials. It is a novel device that provides sustained release of ranibizumab over a 6-month period. The PDS development was a great advancement, but there have been some complications with the device that present a safety issue to patients. The manufacturer is looking to address these problems and will hopefully make an improved version in the near future.

Dr. Rahimy: ARCHWAY was the pivotal phase 3 trial for the PDS with ranibizumab and used ranibizumab as the compariator.[37,39] The part that stands out to me regarding ARCHWAY data through 2 years was the proportion of patients who did not need supplemental or rescue therapy. The data show that a slow, continuous release of ranibizumab works to reduce the injection burden.

Regarding adverse events, anytime we are taking the patient to surgery, we're concerned about endophthalmitis, erosion, and retraction, which had the following rates in the PDS and ranibizumab arms, respectively: 1.6% versus 0.6%, 4.0% versus 0%, and 2.4% versus 0%. Vitreous hemorrhage was a problem with the PDS earlier on in the clinical trials (6.0% vs 3.6%), but this was ameliorated by modifying the surgical technique to include laser ablation of the pars plana. Other ongoing studies on the PDS include PORTAL (NCT03683251), which is the 4-year extension study, and VOYAGER (NCT05476926), which is a global real-world study looking at faricimab and the PDS.[40,41] These results will be reported in the coming years, but initial data from PORTAL show vision maintenance with minimized injections.[42]

Biosimilars

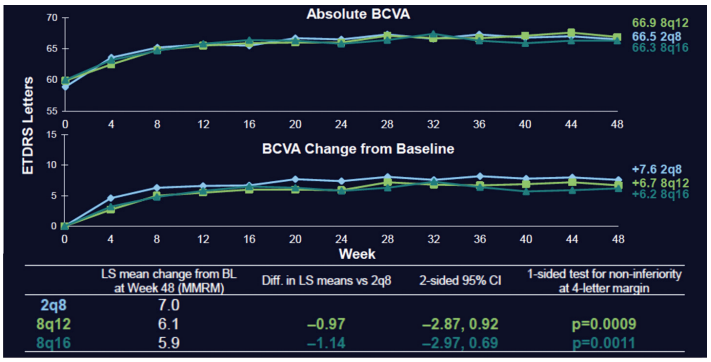
Dr. Rahimy: Finally, we have two FDA-approved biosimilar anti-VEGF agents: ranibizumab-nuna (Byooviz) and ranibizumab-eqrn (Cimerli).[43,44] The FDA granted interchangeability designation to ranibizumab-eqrn.[44] Does this make a difference to you in terms of its use?

Dr. Do: No, it doesn't move the needle much for me. The use of biosimilars is driven more by the payers. So far, the data have shown these to be noninferior with no safety issues.

Dr. Lalwani: I think as we're forced to change due to insurance mandates, we will be forced to become more comfortable with biosimilars. The absence of safety signals is hugely important here and probably the number one thing that we're concerned about.

Dr. Rahimy: Do you think more durable therapies will supplant our first-generation anti-VEGFs?

Dr. Do: In my practice, I am looking forward to the next-generation therapies if they can provide longer disease control. VEGF suppression that can last for a few additional weeks or months will be very beneficial to patients.



	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).ICE, intercurrent events; MMRM, mixed model for repeated measurements

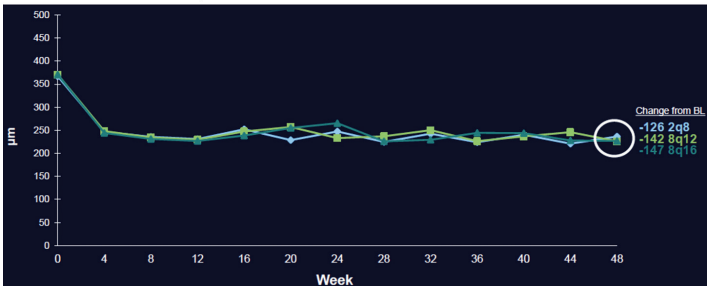


Figure 4. PULSAR: BCVA results and mean change in CRT at 48 weeks.[45]

Dr. Lalwani: I have been impressed with our second-generation agents and am continually evaluating biomarkers to make therapy decision earlier. As far as a surgical intervention, I am looking forward to the PDS coming back to market. My colleagues who have used it have not had complications and have been impressed with how well it's tolerated.

COULD PIPELINE ANTI-VEGF THERAPIES PROVIDE BETTER OUTCOMES?

Dr. Lalwani: There are several new and emerging therapies including high-dose aflibercept and sustained delivery through gene therapy. High-dose aflibercept for nAMD is 8-mg/0.7cc dose, a slightly higher volume. PULSAR compared a fixed-dosing arm of 2-mg aflibercept versus two different arms of 8-mg aflibercept.[45] Initially, all three arms received an injection at baseline, month 1 and month 2. Thereafter, the patients in the 2-mg dose arm received a fixed-dosing regimen of every 8 weeks.

In the 8-mg group, patients were evaluated at week 16 for any kind of disease activity defined as greater than 5-letter loss in BCVA from week 12 BCVA due to persistent or worsening AMD in conjunction with a greater than 25 µm increase in CRT from week 12, or a new onset foveal neovascular or foveal hemorrhage. If there was any disease activity, they were automatically put into a fixed 8-week interval. If there was no disease activity, at week 20 they received an injection and they were put on a Q12-week interval. This interval could be shortened if any of the disease activity criteria were met, whereby they were shortened to an 8-week fixed interval.[45]

It was the same structure for the 8-mg 16-week group. If there was any disease activity, patients were automatically placed into an 8-week fixed interval regimen. If they had no disease activity at week 16 but had disease activity at week 20, then they received an injection at week 20 and were put into a 12-week fixed interval. If no disease activity was noted at either of those time points, they were placed into a 16-week dosing interval, starting at week 24. At any point, if there was any disease activity noted, then patients were moved down by 4 weeks at each time point with a minimum of 8 weeks possible.

At week 48, the BCVA was impressive in all arms, as was the CRT. There was more drying in the 8-mg groups than the 2-mg group (Figure 4).[45]

In the aflibercept 8-mg Q12-week group, 79% of those patients maintained a 12-week interval. Only 21% were brought down to an 8-week interval. In the aflibercept 8-mg 16-week interval group, 77% of those patients were able to maintain a 16-week interval, with 11% moving down to Q12 weeks and 13% moving down to 8 weeks. As a pooled group, 83% of high-dose aflibercept patients achieved a Q12 week or greater interval. Of note, there were no safety signals for the 8-mg group as compared to the 2-mg group. However, when the company put in for their Biologics License Application, the FDA issued a delay in receiving approval.[46] The FDA did not identify any issues with clinical efficacy, safety, trial design, or label of the 8-mg dose, and no additional clinical data or trials have been requested. The company is working with the FDA and a third-party filler to bring aflibercept 8 mg to patients as soon as possible.

Gene Therapy

Dr. Lalwani: There are several gene therapy delivery systems in development. RGX-314 uses an AAV8 vector and is delivered either through suprachoroidal injection or through a vitrectomy with a subretinal treatment. It's being studied for both nAMD and diabetic retinopathy (DR). ADVM-022 uses AAV.7m8 and is an intravitreal injection. It's being studied in nAMD and DME.

Subretinal delivery of RGX-314 for nAMD is being studied in two pivotal trials: ATMOSPHERE (NCT04704921) and ASCENT (NCT05407636).[47,48] The suprachoroidal delivery for RGX-314 is in phase 2 trials for both nAMD (AAVIATE; NCT04514653) and DR (ALTITUDE; NCT04567550).[49,50] These trials are ongoing, but we do have some interim data for AAVIATE.

Cohort 1 (N = 20) was randomized to receive RGX-314 at 2.5x1011 GC/eye through one injection versus ranibizumab. Cohort 2 (N = 20) was randomized to receive RGX-314 at 5x1011 GC/eye through two injections versus ranibizumab. Cohort 3 (N = 20) is evaluating RGX-314 at the same dose level as Cohort 2, but in patients who are NAb positive. Cohort 4 (N = 15) is evaluating RGX-314 at a dose level of 1x1012 GC/eye. Cohort 5 is evaluating the same dose level as Cohort 4 but in 20 patients who are NAb positive. Finally, Cohort 6 is evaluating patients at the same

(Continued on page 13)

CASE 1: PATIENT WITH nAMD AND SUBMACULAR HEMORRHAGE

Dr. Rahimy: Our first case involves an 84-year-old woman who originally came to me for dry AMD. Her baseline VA was 20/30 in the right eye and 20/40 in the left eye. She returned a year later complaining of vague, blurry vision in her right eye, and the VA dropped to 20/50. She's pseudophakic and also had a posterior capsular opacification in the eye, which I thought was contributing to the vision issues. Her OCT revealed low-lying fibrovascular PED with associated exudation. She had subretinal fluid. We initiated three monthly injections of aflibercept in the right eye; the left eye still looks the same and hasn't changed during the year. We extended her to an 8-week interval through year 1 and she underwent a YAG capsulotomy once the disease stabilized. We kept watching the left eye.

Year 2 of therapy, the patient's right eye interval was extended to 12 weeks and her VA remained stable at 20/20 OD and 20/40 OS. She went on apixaban and shortly thereafter presented with a massive submacular hemorrhage in her left eye and was counting fingers at 2 ft (Figure 1). What are your next steps?

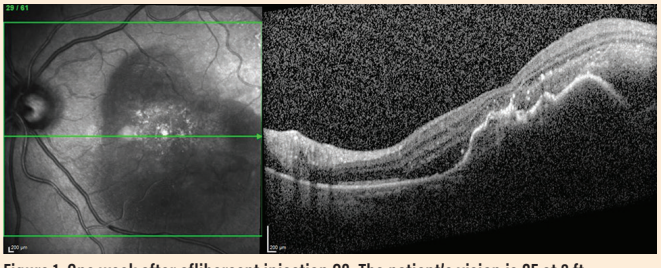


Figure 1. One week after aflibercept injection OS. The patient's vision is CF at 2 ft.

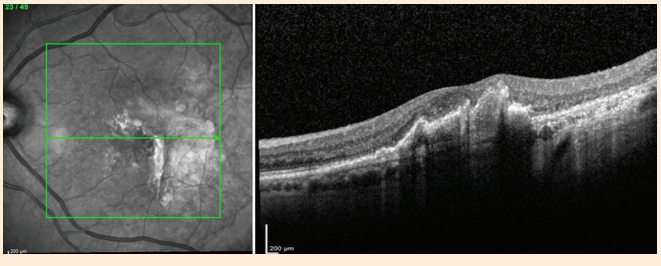


Figure 2. Status post aflibercept x8 (now at 8-week interval). The patient's VA OS is 20/50.

Images courtesy of Ehsan Rahimy, MD

Dr. Lalwani: Given her age and the unpredictable vision potential of submacular hemorrhages I would lean toward injecting more often over surgery.

Dr. Rahimy: She elected for injections of aflibercept. A month later, she's already 20/200 and we're seeing improved anatomy each time. After her second injection, her VA was 20/100 and most of the exudation was gone. Eventually her vision settled into the 20/60, 20/80 range. Her VA was 20/50 after eight injections and well maintained on an extended treatment interval (Figure 2).

CASE 2: HIGH-INJECTION BURDEN WITH PERSISTENT PED

Dr. Lalwani: Our second case involves a patient with a history of nAMD who had already been treated with seven injections of bevacizumab and three injections of aflibercept. He had a large PED with a little bit of fluid at the base. VA was 20/40 (Figure1). We decided to continue with aflibercept, and 1 month later the PED started flatting and his VA improved to 20/20. We continued with injections, and he had a recurrent PED later that year. His VA dropped to 20/25. His course and clinical appearance were most consistent with type I choroidal neovascularization (CNV). We injected monthly, but he still had subretinal fluid and a PED. His VA continued to be quite good—20/25, 20/30. Several years later, he developed CME in conjunction with a mild epiretinal membrane. We decided against surgery to remove it, given the uncertain vision potential.

Over time we observed increased subretinal material accumulating under the subretinal fluid and a persistent PED. Desperate to resolve the fluid, we even tried dexamethasone. He has received more than 30 injections of aflibercept. We switched him to faricimab in May 2022 and, after five injections, there has been a resolution of the subretinal fluid, the CME, and the PED. However, the interval has only increased to 6 weeks. Would either of you have considered surgery to remove that epiretinal membrane?

Dr. Do: He's having a great response to just the pharmacologic therapy. Sometimes I worry a vitrectomy will alter the pharmacokinetics of a drug and make it less durable. I would try to avoid surgery if possible.

Dr. Lalwani: I saw him in June 2023, and we've increased his interval to 5 or 6 weeks. There's now an increase in CME, a little bit of subretinal fluid, and the PED is back (Figure 2). His vision still is about the same. What would you do?

Dr. Rahimy: I think you continue with the current therapy, and hopefully we may have high-dose aflibercept available to us in the near future as another option to try.

Dr. Lalwani: This case illustrates a nice evolution of anti-VEGF therapy over 10 years. It's impressive that he has not developed a significant amount of macular atrophy.

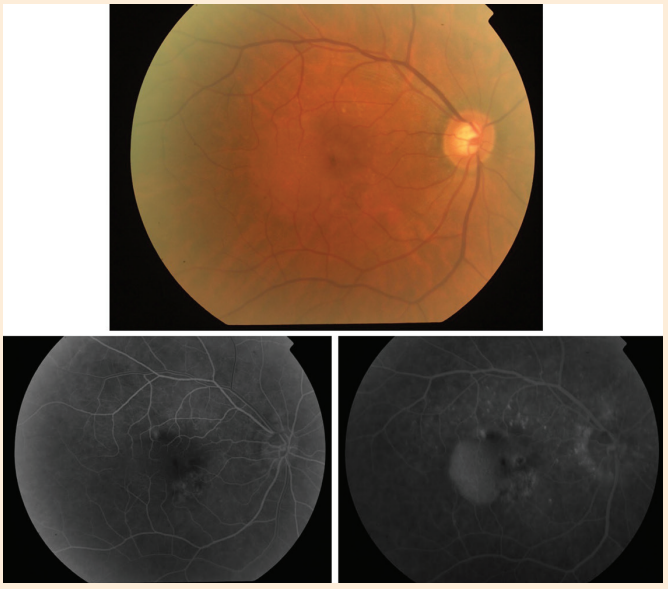


Figure 1. The patient received seven injections of bevacizumab and three injections of aflibercept. He had a large PED with a small amount of fluid at the base. His VA was 20/40.

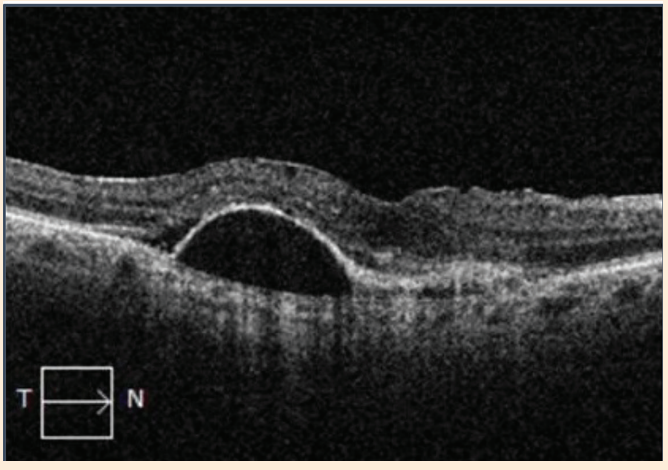


Figure 2. During the patient's last visit, we increased his interval to 5 or 6 weeks. There is now an increase in CME, some subretinal fluid, and the PED returned.

Images courtesy of Geeta A. Lalwani, MD

(Continued from page 11)
dose level as Cohorts 4 and 5 and includes a short course of prophylactic steroids following administration of RGX-314.[51] RGX-314 was well-tolerated in Cohorts 1 to 5 (N = 85) with follow-up ranging from 1 to 12 months post-dosing. In Cohort 4, 67% of patients did not need rescue therapy, which is quite impressive with a single dose out to 6 months. Of note, there were no major safety signals for any of these patients. The NAb-positive patients had no significant meaningful difference in their outcomes.[51]

Dr. Do: Dr. Lalwani, what are your main considerations for incorporating a new therapy in your clinical practice?

Dr. Lalwani: We're limited by insurance, but safety is my primary concern. As illustrated by the issues with brolucizumab, we all need to wait a bit post-market to see what happens.

Dr. Do: Which patients would you most likely treat with the next generation of retinal therapies if or when they become available?

Dr. Lalwani: Like most specialists, suboptimal responders or patients with short intervals are my ideal switches. I examine whether the patient will do better switching to a new agent, or will the response be about the same? It is truly exciting to see the myriad potential therapies in the pipeline, with potentially more potent treatments as well as longer duration coming. Physicians can look forward to having more tools to help take care of their patients. ■

1. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of Age-Related Macular Degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140(12):1202-1208.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444.
4. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145(2):239-248.
5. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.
6. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046-1056.
7. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology*. 2010;117(11):2134-2140.
8. Managing Neovascular (Known as "Wet") Age-related macular degeneration over 2 years using different treatment schedules of 2 mg intravitreal aflibercept injected in the eye (ARIES). ClinicalTrials.gov ID: NCT02581891. https://clinicaltrials.gov/study/NCT02581891. Updated May 21, 2020. Accessed August 15, 2023.
9. Ohji M, Takahashi K, Okada AA, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR: a randomized controlled trial. *Adv Ther*. 2020;37(3):1173-1187.
10. Mitchell P, Holz FG, Hykin P, et al. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: The ARIES Study: a randomized clinical trial [published correction appears in Retina. 2022;42(9):e43]. *Retina*. 2021;41(9):1911-1920.
11. Ohji M, Lanzetta P, Korobelnik JF, et al. Efficacy and treatment burden of intravitreal aflibercept versus intravitreal ranibizumab treat-and-extend regimens at 2 years: network meta-analysis incorporating individual patient data meta-regression and matching-adjusted indirect comparison. *Adv Ther*. 2020;37(5):2184-2198.
12. Wolf S, Holz FG, Midena E, et al. Patients with neovascular age-related macular degeneration requiring intensive intravitreal aflibercept treatment: An ARIES Post hoc analysis. *Ophthalmol Ther*. 2022;11(5):1793-1803.
13. Okada AA, Takahashi K, Ohji M, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in the altair study: 96-week outcomes in the polypoidal choroidal vasculopathy subgroup. *Adv Ther*. 2022;39(6):2984-2998.
14. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723-734.
15. Core JQ, Pistilli M, Daniel E, et al. Predominantly persistent subretinal fluid in the comparison of age-related macular degeneration treatments trials. *Ophthalmol Retina*. 2021;5(10):962-974.
16. Sadda S, Holekamp NM, Sarraf D, et al. Relationship between retinal fluid characteristics and vision in neovascular age-related macular degeneration: HARBOR post hoc analysis. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(12):3781-3789.
17. Ciulla TA, Hussain RM, Pollack JS, Williams DF. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients: a real-world analysis of 49 485 eyes. *Ophthalmol Retina*. 2020;4(1):19-30.
18. Khanani AM, Skelly A, Bezlyak V, Griner R, Torres LR, Sagkriotis A. SIERRA-AMD: A retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2020;4(2):122-133.
19. Kiss S, Campbell J, Almony A, et al. Management and outcomes for neovascular age-related macular degeneration: analysis of united states electronic health records. *Ophthalmology*. 2020;127(9):1179-1188.
20. Baumal CR. Wet age-related macular degeneration: treatment advances to reduce the injection burden. *Am J Manag Care*. 2020;26(5 Suppl):S103-S111.
21. Giocanti-Aurégan A, García-Layana A, Peto T, et al. Drivers of and barriers to adherence to neovascular age-related macular degeneration and diabetic macular edema treatment management plans: a multi-national qualitative study. *Patient Prefer Adherence*. 2022;16:587-604.
22. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398.
23. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration [published correction appears in Ophthalmology. 2013;120(1):209-10]. *Ophthalmology*. 2012;119(12):2537-2548.
24. Bhisitkul RB, Mendes TS, Rofagha S, et al. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. *Am J Ophthalmol*. 2015;159(5):915-24.e2.
25. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Devel Ther*. 2016;10:1857-1867.
26. Novartis. Beovu Package Insert. https://www.novartis.com/us-en/sites/novartis_us/files/beovu.pdf. Revised December 2022. Accessed August 15, 2023.
27. Genentech. Susvimo Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761197s000lbl.pdf. Revised October 2021. Accessed August 15, 2023.
28. Genentech. VABYSMO Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf. Revised January 2022. Accessed August 15, 2023.
29. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: Ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration [published correction appears in Ophthalmology. 2022 May;129(5):593-596]. Ophthalmology. 2021;128(1):89-99.
30. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84.
31. MacCumber MW, Wykoff CC, Karcher H, et al. One-year brolucizumab outcomes in neovascular age-related macular degeneration from a large united states cohort in the IRIS Registry [published online ahead of print, 2023 Apr 21]. *Ophthalmology*. 2023;S0161-6420(23)00277-4.
32. MacCumber MW, Wykoff CC, Karcher H, et al. Factors linked to injection interval extension in eyes with wet age-related macular degeneration switched to brolucizumab. *Ophthalmology*. 2023;130(8):795-803.
33. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399(10326):729-740.
34. Khanani AM. Faricimab in neovascular age-related macular degeneration: year 2 efficacy, safety, and durability results from the phase 3 TENAYA and LUCERNE Trials. 2022 ASRS Annual Meeting; New York, NY.
35. Khanani AM, Aziz AA, Khan H, et al. The real-world efficacy and safety of faricimab in neovascular age-related macular degeneration: the TRUCKEE study - 6 month results. *Eye (Lond)* 2023.
36. Leung EH, Oh DJ, Alderson SE, et al. Initial real-world experience with faricimab in treatment-resistant neovascular age-related macular degeneration. *Clin Ophthalmol*. 2023;17:1287-1293.
37. Holekamp NM, Campochiaro PA, Chang MA, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2022;129(3):295-307.
38. Genentech. Voluntary recall of the SUSVIMO Ocular Implant. https://www.gene.com/download/pdf/Susvimo_DHCP_Important_Prescribing_Information_2022-10-18.pdf. Published October 2022. Accessed August 15, 2023.
39. Regillo C, Berger B, Brooks L, et al. Archway phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration 2-year results. *Ophthalmology*. 2023;130(7):735-747.
40. Extension Study for the Port Delivery System With Ranibizumab (Portal). ClinicalTrials.gov ID: NCT03683251. https://clinicaltrials.gov/study/NCT03683251. Updated August 8, 2023. Accessed August 15, 2023.
41. A real-world study to gain clinical insights into Roche ophthalmology products (VOYAGER). ClinicalTrials.gov ID: NCT05476926. https://clinicaltrials.gov/study/NCT05476926. Updated August 15, 2023. Accessed August 15, 2023.
42. Charters L. Angiogenesis, Exudation and Degeneration 2022: Spotlighting major advances in retinal diagnostics and therapies. https://europe.ophthalmologytimes.com/view/angiogenesis-exudation-and-degeneration-2022-spotlighting-major-advances-in-retinal-diagnostics-and-therapies. Published March 4, 2022. Accessed August 15, 2023.
43. Biogen. Biogen and Samsung Bioepis' BYOOVIZ (ranibizumab-nuna) launches in the United States. https://www.globenewswire.com/en/news-release/2022/06/02/2455159/0/en/Biogen-and-Samsung-Bioepis-BYOOVIZ-ranibizumab-nuna-Launches-in-the-United-States.html. Published June 2, 2022. Accessed August 15, 2023.
44. Polphara Biologics. U.S. Food and Drug Administration (FDA) approves FYB201/CIMERLI® (ranibizumab-eqrn), the first and only biosimilar interchangeable with Lucentis. https://polpharmabiologics.com/en/knowledge/latest-news/article/u-s-food-and-drug-administration-fda-approves-fyb201-cimerlitm-ranibizumab-eqrn-the-first-and-only-biosimilar-interchangeable-with-lucentis-r. Published March 8, 2022. Accessed August 15, 2023.
45. Lanzetta P. Intravitreal aflibercept injection 8 mg for nAMD: 48-week results from the phase 3 PULSAR Trial. 2022 American Academy of Ophthalmology Annual Meeting; September 30-October 2, 2022; Chicago, IL.
46. Regeneron Pharmaceuticals I. FDA issues complete response letter (CRL) for aflibercept 8 mg biologics license application solely due to an ongoing review of inspection findings at a third-party filler. https://investor.regeneron.com/news-releases/news-release-details/fda-issues-complete-response-letter-crl-aflibercept-8-mg. Published June 27, 2023. Accessed August 15, 2023.
47. Pivotal 1 study of RGX-314 gene therapy in participants with nAMD (ATMOSPHERE). ClinicalTrials.gov ID: NCT04704921. https://clinicaltrials.gov/study/NCT04704921. Updated May 22, 2023. Accessed August 15, 2023.
48. Pivotal 2 study of RGX-314 gene therapy in participants with nAMD (ASCENT). ClinicalTrials.gov ID: NCT05407636. https://clinicaltrials.gov/study/NCT05407636. Updated June 12, 2023. Accessed August 15, 2023.
49. RGX-314 gene therapy administered in the suprachoroidal space for participants with diabetic retinopathy (DR) without center involved-diabetic macular edema. ClinicalTrials.gov ID: NCT04567550. https://clinicaltrials.gov/ct2/show/NCT04567550. Updated May 22, 2023. Accessed August 15, 2023.
50. RGX-314 gene therapy administered in the suprachoroidal space for participants with neovascular age-related macular degeneration (nAMD) (AAVIATE). ClinicalTrials.gov Identifier: NCT04514653. https://clinicaltrials.gov/ct2/show/NCT04514653. Updated May 22, 2023. Accessed August 15, 2023.
51. Regenxbio. REGENXBIO announces additional positive interim data from trials of RGX-314 for the treatment of wet AMD. https://www.prnewswire.com/news-releases/regenxbio-announces-additional-positive-interim-data-from-trials-of-rgx-314-for-the-treatment-of-wet-amd-301638557.html. Published October 3, 2022. Accessed August 15, 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**
Describe the current treatments available to treat neovascular age-related macular degeneration (nAMD)	_____	_____	_____
Discuss the considerations involved in the choice of anti-VEGF agent and tailoring treatment regimens for individual patients	_____	_____	_____
Evaluate clinical evidence for biomarkers that are prognostic of optimal visual outcomes	_____	_____	_____
Summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in nAMD	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to summarize the advances in VEGF inhibition that may improve treatment outcomes and/or treatment burden in 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. According to treat-and-extend trials of anti-VEGF dosing for nAMD, what percentage of patients were able to achieve treatment intervals of at least 12 weeks?

A. ~20%
B. ~30%
C. ~40%
D. >50%

3. A 68-year-old patient presents to your clinic for initial evaluation. She has a history of recurrent anterior iridocyclitis and AMD. She notes recent onset of blurry vision in her right eye. On examination you note a normal exam except for subretinal hemorrhage OD and her OCT has evidence of new cystic intraretinal fluid. What is the next appropriate step in management of this patient?

A. Observation
B. Initiate topical prednisolone four times a day
C. Initiate intravitreal aflibercept treatment
D. Initiate intravitreal steroid treatment

4. A 68-year-old patient with nAMD presents to your clinic for follow-up. She has had improvement in both BCVA and OCT anatomy on monthly aflibercept; however, she still has intraretinal fluid present in her macula. You discuss switching to faricimab with this patient. All of the following statements about faricimab are true EXCEPT:

A. Studies have shown a decrease in central subfield thickness (CST) after switching to faricimab
B. Studies have shown an increase in CST after switching to faricimab
C. Studies have shown significantly longer mean dosing intervals with faricimab than ranibizumab or aflibercept
D. Studies have shown improved BCVA after switching to faricimab

5. An 86-year-old White man presents to your office for evaluation. You diagnose him with nAMD and recommend he start monthly anti-VEGF treatment. He has Medicaid insurance and is worried about his ability to pay for treatments and about the pain of injections. All of the following include risk factors for loss to follow-up for this patient EXCEPT:

A. Age
B. White race
C. Medicaid insurance
D. Fear of injections

6. You are evaluating a 75-year-old patient with nAMD. She has experienced recurrent intraretinal fluid despite monthly ranibizumab as well as aflibercept. She has a history of recurrent intraocular inflammation. What is the next most reasonable treatment option?

A. Switch to brolucizumab
B. Switch to faricimab
C. Inject intravitreal corticosteroids
D. Perform photodynamic therapy

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.

_____

_____