CME MONOGRAPH

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LESS IS MORE

Reducing Injections and Optimizing Vision With Anti-VEGF Therapy for nAMD, DR, and DME

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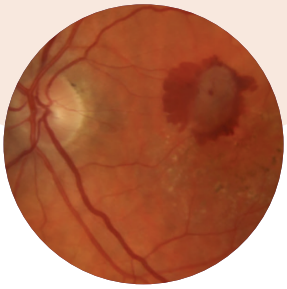

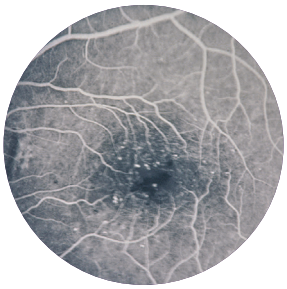

FACULTY

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This continuing medical education activity is provided by MedEdicus LLC.

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Activity Description and Purpose

This educational activity will provide clinicians with insights on the most relevant clinical data for treating wet age-related macular degeneration and diabetic retinopathy/diabetic macular edema. Experts in the field will discuss ways to extend the treatment interval and individualize care in patients who suffer from these sight-threatening diseases. The desired results of this activity are to help clinicians optimize patient care by giving them information that helps them understand the place in therapy of novel and new agents that may decrease treatment burden through extending the treatment interval.

Target Audience

This educational activity is intended for retina specialists and other ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Describe the latest clinical data for anti-VEGF treatments for wet age-related macular degeneration
- Describe the latest clinical data for anti-VEGF treatments for diabetic retinopathy/diabetic macular edema
- Individualize care to effectively extend the treatment interval in patients with wet age-related macular degeneration
- Individualize care to effectively extend the treatment interval in patients with diabetic retinopathy/diabetic macular edema

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* The financial relationship existed during the past 24 months but has now ended

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LESS IS MORE

Reducing Injections and Optimizing Vision With Anti-VEGF Therapy for nAMD, DR, and DME

Introduction

The disease burden for patients with neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), and diabetic macular edema (DME) is significant and far reaching. Loss of vision can lead to impairment in patients' ability to read, drive, and recognize faces.[1] Many patients are older, may live alone, and may have difficulty performing their activities of daily living.[1,2] They are often at greater risk for falls and may experience social isolation and depression.[3-5]

Treatment with anti–vascular endothelial growth factor (VEGF) therapy has helped many patients improve their vision and quality of life (QOL). Anti-VEGF treatment, however, may come with significant psychosocial, time-related, and financial burdens. For example, patients may have anxiety before and during treatment.[6,7] They may experience adverse effects and require time off from work or other activities. Many patients also require assistance from a caregiver for transportation and additional care related to their injections.[6,8] Finally, the financial cost associated with treatment can be significant.[7]

Real-world studies have demonstrated that patients receiving anti-VEGF treatments often experience worse visual outcomes than those enrolled in clinical trials.[9-11] Several reasons may account for these differences. Patients in real-world practice often have a wider variety of clinical presentations and may have more severe disease.[9] Undertreatment is also a factor. Undertreatment can be due to nonadherence, which is a deviation from the planned treatment regimen[9,12]; it can also be related to nonpersistence, which is complete discontinuation of treatment or loss to follow-up.

The rates of nonadherence and nonpersistence in nAMD treatment have been as high as 60% after 2 years in some studies.[13] The risks of disease recurrence and vision loss have been demonstrated to increase with treatment intervals > 12 and 16 weeks, respectively, with older anti-VEGF agents.[14]

There are various possible reasons for treatment nonadherence and nonpersistence **(Table)**.[13] Patient factors, such as worse baseline visual acuity (VA), greater travel distance to the treating provider, lack of transportation, and medical comorbidities, are often involved.[13] Treatment efficacy is also important, with greater improvement in vision from treatment correlated with better adherence and persistence. Treatment cost may also be a factor in some instances. Finally, the burden of fixed dosing regimens with frequent injections can lead to nonadherence and nonpersistence.[12] Thus, clinicians are challenged with finding a balance between reducing treatment frequency enough to improve the burden for patients and treating frequently enough to optimize efficacy.[10]

Clinicians administering anti-VEGF injections experience significant burdens on time, resources, and staff usage.[8] As such, a reduced injection frequency would benefit patients and providers alike. In the United States, two-thirds of retina specialists identified a longer treatment interval as the most important success metric for anti-VEGF agents.[15]

To address the burdens of both patients and clinicians, treat-and-extend (TAE) and as-needed dosing protocols are commonly used in real-world clinical practice to extend the intervals between anti-VEGF treatments.[10] For nAMD, TAE protocols have been demonstrated to achieve better VA outcomes than as-needed protocols, but are associated with a greater number of injections.[16] This advantage is less clear for DME, with 2 recent meta-analyses suggesting similar outcomes for TAE and as-needed protocols.[17,18] The optimal dosing strategy has yet to be defined and may vary depending on the treatment used and individual patient factors. Multiple new studies have investigated new treatments that may allow for extended dosing intervals.

Table. Possible Factors Increasing Risk for Anti–Vascular Endothelial Growth Factor Treatment Nonadherence and Nonpersistence in Neovascular Age-Related Macular Degeneration[13]

Condition-Related Factors	Patient-Related Factors	Treatment-Related Factors	Health Systems–Related Factors	Socioeconomic Factors
• Worse baseline VA • Bilaterality • No change in VA with treatment • Worse final VA	• Older age • Non-White ethnicity • Systemic comorbidities • Fear of injections • Perception that injections are not needed or do not work • Loss of motivation	• Increased treatment burden/injection frequency • Nonindividualized treatment regimen • Increased frequency of follow-up visits • Needing to schedule separate appointments for assessment and injections	• Lack of information • Lack of trust in physician • Longer distance of travel to treatment • Appointment difficulties	• Lower socioeconomic status • Social isolation or lack of caregiver • Lack of insurance • Financial burden • Lack of transportation

Abbreviation: VA, visual acuity.

In this educational activity, retina specialists Katherine Talcott, MD, Zelia M. Correa, MD, PhD, and Jessica Randolph, MD, will discuss cases and their perspectives on safely extending treatment intervals in nAMD and DR/DME with new treatments, including high-dose (HD) (8 mg) aflibercept and dual-mechanism (anti-VEGF and angiopoietin-2) faricimab. Following this, they will share clinical pearls for counseling patients.

Neovascular Age-Related Macular Degeneration: Review of Clinical Trials

Without treatment, the prognosis of nAMD is poor, with approximately 40% of patients developing severe vision loss within 3 years.[19] Similarly, inadequate treatment can have a negative impact on visual outcomes. For example, delayed or interrupted treatment due to the COVID-19 pandemic was associated with worse short-term best-corrected VA (BCVA).[20]

Early anti-VEGF therapies for nAMD were dosed monthly. Ranibizumab was approved in 2006 following the MARINA and ANCHOR phase 3 trials, which demonstrated the efficacy of monthly ranibizumab compared with verteporfin photodynamic therapy.[21-23] Subsequent trials investigating less-frequent dosing demonstrated reduced efficacy.[24,25] Ranibizumab is currently approved for extended dosing intervals of every 3 months or 4 to 5 doses on average over 9 months.[26] Two ranibizumab biosimilars, ranibizumab-nuna and ranibizumab-eqrn, are currently US Food and Drug Administration (FDA) approved.[21] Adverse events for ranibizumab include rare risks of endophthalmitis, increase in intraocular pressure (IOP), and arterial thromboembolic events.[26]

Aflibercept 2 mg was approved for the treatment of nAMD in 2011, with an 8-week dosing interval following an initial loading dose once a month for 3 months.[21] The VIEW1 and VIEW2 phase 3 trials demonstrated noninferiority of this regimen compared with monthly ranibizumab.[27] Aflibercept 2 mg was well tolerated, with a safety profile similar to that of ranibizumab.

Bevacizumab, which is approved for the treatment of colorectal cancer, became an off-label first-line treatment for nAMD after the ranibizumab trials and continues to be used.[21] Several trials evaluated the efficacy of bevacizumab for nAMD, and VA outcomes and safety were shown to be similar to those of ranibizumab across different dosing protocols.[28]

The Comparison of Age-Related Macular Degeneration Treatments Trials, which evaluated ranibizumab, aflibercept, and bevacizumab for nAMD, found that very few patients remained on their dosing protocols; vision gains in the first 2 years were not maintained at 5 years.[29] Mean VA at 5 years declined to less than that at baseline; however, half of the patients still had good VA at 5 years, demonstrating that anti-VEGF therapy can be successful.

To help reduce injection frequency with these anti-VEGF agents, as-needed and TAE protocols were devised. The switch from fixed dosing to an as-needed regimen (with ranibizumab) early on was associated with declines in VA.[30] Thus, there was a need for improved treatments and dosing protocols, in which intervals could be safely extended without compromised effectiveness. Further studies of TAE protocols with drugs such as ranibizumab and aflibercept have demonstrated noninferior functional and anatomical outcomes, with reduced treatment burden.[16,31-33]

Treat-and-Extend With Ranibizumab: CANTREAT

CANTREAT (Canadian Treat-and-Extend Analysis Trial) and its open-label extension study evaluated the ability to extend ranibizumab 0.5-mg dosing beyond 4 weeks to intervals of up to 12 weeks.[34-36] The TAE protocol was to extend from injections every 4 weeks by 2-week intervals until a maximum of 12 weeks if disease remained stable. If disease instability occurred, intervals were decreased by 2 weeks until the patient was stable. Visual acuity and central retinal thickness (CRT) were improved and maintained throughout the 24 months in the original study and through 36 months in most patients who continued treatment in the open-label extension. Safety was comparable with that of the 4-week regimen.

Treat-and-Extend With Aflibercept 2 mg: ALTAIR and ARIES

Recent clinical trials have investigated the ability to extend aflibercept 2-mg dosing to intervals beyond 8 weeks using TAE protocols. The ALTAIR phase 4 trial aimed to determine the optimal TAE protocol with aflibercept 2 mg.[37] The trial evaluated dosing intervals from 8 to 16 weeks, with adjustments at 2- and 4-week increments. Visual acuity and CRT were improved and maintained throughout the 96-week study period. At week 96, approximately 60% of 246 patients achieved a treatment interval ≥ 12 weeks. Outcomes were similar for both the 2- and 4-week dosing interval adjustments. Safety was also similar between the 8-week and extended regimen.

The ARIES phase 3b/4 trial further evaluated TAE regimens with aflibercept 2 mg.[38] In this trial, following 4 monthly loading doses, an early-start TAE protocol was compared with a late-start TAE protocol. In the early-start protocol, 2-week interval adjustments began at week 16. In the late-start protocol, 8-week fixed intervals were continued to week 48, at which point 2-week adjustments began. Both protocols resulted in improved functional and anatomical outcomes at week 104. Outcomes for BCVA, CRT, and number of injections were similar between the 2 protocols, with a mean of 12 and 13 injections at 2 years for early and late start, respectively.

Agents With Extended Treatment Intervals: Brolucizumab and Ranibizumab Port Delivery System

Newer treatments that allow for extended treatment intervals have emerged. Brolucizumab was FDA approved for the treatment of nAMD in 2019.[21] The HAWK and HARRIER phase 3 trials demonstrated noninferiority of brolucizumab to aflibercept for this indication.[39] In these trials, > 50% of patients receiving

brolucizumab maintained a dosing interval of 12 weeks up to week 48 of treatment. Despite its efficacy, brolucizumab carries an elevated risk of intraocular inflammation that has limited its use.[40]

The ranibizumab port delivery system (PDS) is a refillable intravitreal device that is surgically implanted and offers sustained release of drug over 24 weeks.[21] This system has the benefit of avoiding the need for frequent intravitreal injections. Associated risks include endophthalmitis (2%), hypotony (6%), and vitreous hemorrhage (5%).[41] The PDS was FDA approved for nAMD in 2021 following the Archway trial, which demonstrated noninferiority of ranibizumab PDS to monthly ranibizumab.[21,42] In 2022, implantation of the PDS device was halted because of a recall of the implant and insertion tool kit based on reports of dislodgement of the device's septum after refill procedures.[21,43] Refill-exchange procedures are still allowed for patients who already have the implant.

Novel and New Treatments: High-Dose Aflibercept and Faricimab

Most recently, aflibercept HD and faricimab became available as new options for optimizing vision gains and fluid resolution while extending treatment intervals.[44,45]

An 8-mg HD version of aflibercept was approved for treatment of nAMD (and DME) in 2023, allowing for dosing intervals of up to 16 weeks.[44,46] This provides a desirable option for clinicians who are comfortable with the safety profile of aflibercept 2 mg, but want to extend the dosing interval for their patients. Aflibercept HD was studied in the PULSAR trial, which evaluated the noninferiority of aflibercept 8 mg at 12- and 16-week dosing intervals to standard aflibercept 2 mg at an 8-week dosing interval in treatment-naïve patients with nAMD.[44,47] The primary study end point was achieved, with noninferior VA outcomes for aflibercept 8 mg (HD).[44] At week 48, 83% of patients in the aflibercept HD group maintained dosing intervals ≥ 12 weeks **(Figure 1)**.[44] At week 16, the proportion of patients with no intraretinal fluid (IRF) or subretinal fluid (SRF) in the central subfield was greater for aflibercept HD (63%) than for aflibercept 2 mg (52%). In a subgroup analysis of baseline BCVA, central subfield retinal thickness (CST), and lesion type, BCVA improvement was seen in all groups and was similar between aflibercept HD and aflibercept 2 mg.[48] Serious adverse events were similar between aflibercept HD and aflibercept 2 mg and included rare risks of IOP increase, intraocular inflammation, and endophthalmitis.[44,49]

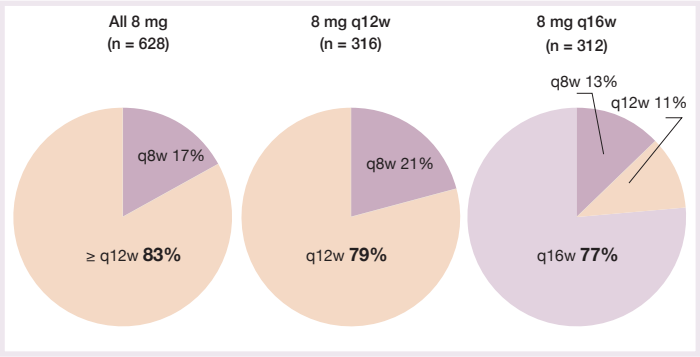

Figure 1. Extended dosing intervals in the PULSAR phase 3 trial with aflibercept 8 mg.[44] At week 48, 83% of patients maintained dosing intervals of at least 12 weeks.

Abbreviations: q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks.

Faricimab: TENAYA, LUCERNE, FARETINA-AMD, TRUCKEE

Faricimab is a bispecific antibody targeting VEGF-A and angiopoietin-2 that was approved for the treatment of nAMD in 2022.[21] This provides a desirable option for clinicians who have patients whom they feel would benefit from a dual mechanism of action. Angiopoietin-2 increases vascular permeability and potentiates the effects of VEGF. In the TENAYA and LUCERNE trials for nAMD, after an initial loading phase, faricimab administered at intervals of up to 16 weeks was compared with aflibercept 2 mg administered every 8 weeks.[45] Faricimab demonstrated noninferiority to aflibercept for the primary study end point of mean change in BCVA. Approximately 80% and 45% of 631 patients treated with faricimab achieved dosing intervals ≥ 12 or 16 weeks, respectively **(Figure 2)**.[45] Reductions in CST were similar to those with faricimab dosed up to 16 weeks and aflibercept. In the dose-matched phase, however, greater reduction in CST from baseline was achieved with faricimab.[50] Serious adverse events were similar between the faricimab and aflibercept groups and included rare risks of IOP increase, intraocular inflammation, and endophthalmitis.[45]

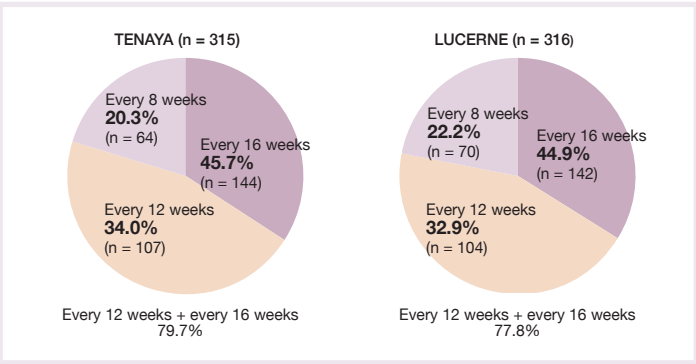

Figure 2. Proportion of patients treated with faricimab with 8-, 12-, and 16-week dosing intervals in the TENAYA and LUCERNE phase 3 trials.[45] Approximately 80% of patients achieved dosing intervals ≥ 12 weeks at week 48.

Reprinted from *The Lancet*, 399, Heier JS, Khanani AM, Ruiz CQ, 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, 729-740, Copyright 2022, with permission from Elsevier.

Because clinical trials are often restricted to treatment-naïve patients and to those without certain comorbidities, real-world studies can improve understanding of the response to treatment in actual clinical practice.[51] In the retrospective FARETINA-AMD study, real-world data from the Intelligent Research in Sight registry for > 12,000 eyes with nAMD treated with faricimab were analyzed.[52] This included 86.5% of eyes that were previously treated. Mean change in best-documented VA after 4 injections was 0.5 letters and 1.6 letters in previously treated and treatment-naïve groups, respectively. In both groups, approximately 55% of eyes achieved an extended dosing interval (> 6 weeks) after 2 injections.[53]

The TRUCKEE study was a multicenter retrospective review of 376 eyes treated with faricimab, 90% of which were previously treated.[51] This included 63% of eyes that were previously treated with aflibercept. Both previously treated and treatment-naïve eyes demonstrated improvements in VA, IRF, SRF, and pigment epithelial detachments (PEDs) after 1 and 3 injections of faricimab. The authors recommended initial treatment with 3 monthly injections or maintenance at the previous dosing interval for 3 injections before extending the dosing interval of faricimab.

Case Presentations in Age-Related Macular Degeneration

Case 1: Differentiation of Age-Related Macular Degeneration From Central Serous Chorioretinopathy

From the Files of Katherine Talcott, MD

A 74-year-old woman who was a smoker presented with a report of a "smudge" that had been in her right eye for 1 week. She had a history of a steroid injection in her right hip 6 weeks prior. Visual acuity was 20/40 OD and 20/25 OS. Optical coherence tomography (OCT) image of the right eye revealed SRF and hyperreflective material at the level of the retinal pigment epithelium ***(Figure 3A)****. OCT image of the left eye revealed drusen* ***(Figure 3B)****. OCT angiography image did not reveal flow over this area to suggest choroidal neovascularization* ***(Figure 3C)****. The differential diagnosis included nAMD or central serous chorioretinopathy (CSR). The decision was made to monitor closely.*

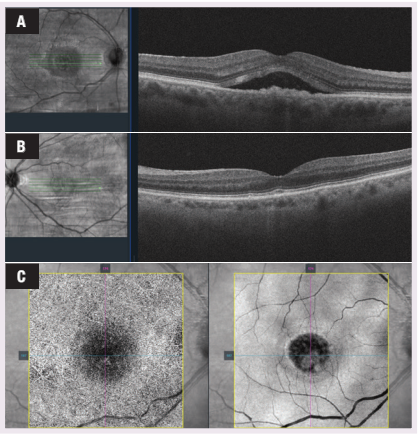

Figure 3. Initial images of the patient presented in Case 1: (A) Optical coherence tomography (OCT) image of the right eye revealed subretinal fluid and hyperreflective material at the level of the retinal pigment epithelium; (B) OCT image of the left eye revealed drusen; (C) OCT angiography images of the right eye did not reveal flow to indicate choroidal neovascularization

Images courtesy of Katherine Talcott, MD

At the 3-week follow-up, VA had decreased and fluid on OCT had increased ***(Figure 4A)****. Treatment with bevacizumab was initiated. Four weeks after bevacizumab injection, vision had improved to 20/25 OD* ***(Figure 4B)****. After a series of injections at 4- to 5-week intervals, residual fluid was still present* ***(Figure 4C)****. The decision was made to change treatment to faricimab, and a series of 3 injections was administered every 4 to 5 weeks, with resolution of the residual fluid* ***(Figures 4D and 4E)****.*

Dr Talcott: I felt a little confused and stuck after the series of bevacizumab injections. The diagnosis could still have been CSR with some residual fluid or it could have been nAMD with persistent fluid. One of the things I considered was switching to an agent that might be able to dry the patient out a little better in order to test whether it was an exudative process or not.[50,51,54]

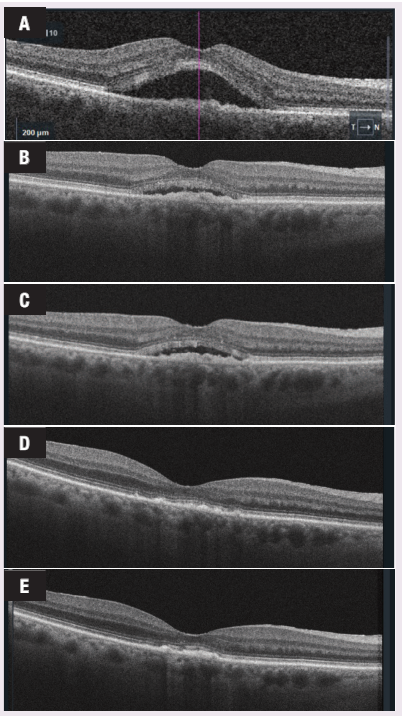

Figure 4. Follow-up optical coherence tomography images of the right eye of the patient in Case 1: (A) after 4 weeks of initial observation without treatment; (B) 4 weeks after initiation of treatment with bevacizumab; (C) after a series of 4 bevacizumab injections at 4- to 5-week intervals; (D) 4 weeks after changing treatment to faricimab; and (E) after 3 faricimab injections extended to 7-week intervals

Images courtesy of Katherine Talcott, MD

So I switched her to faricimab. Aflibercept HD was not available at the time, but that would have been a consideration.[44] Both agents have data that show a strong drying effect.[44,50,51,54]

I am really curious to hear your thoughts on this case. Have you ever encountered this situation before?

Dr Randolph: Yes, similar to you, I tend to start with short-term observation and see if the condition changes. The only other thing that I would have considered in the workup would be traditional fluorescein angiography (FA) to look for the late leakage that you get with CSR. The drusen in the other eye makes it a little bit more concerning for nAMD. You did a good number of the regular 4- to 6-week bevacizumab injections, and nothing really happened. Therefore, switching to the stronger drying agent faricimab was a smart play there.[50,51,54,55]

Dr Correa: I get a lot of these very challenging cases. Many of these CSR cases have some retinal pigment epithelium changes that are sometimes very tough to detect. When I am unsure looking at the OCT images, FA can be very helpful. Obviously, we are moving away from FA, but I think in these cases, it is still the gold standard. Your approach is exactly what I would have done.

Dr Talcott: The other thing that I was curious about on this case is that there has been much recent data to suggest that patients can sometimes tolerate some SRF.

How tolerant are you to some persistent SRF?

Dr Randolph: I tend to start with bevacizumab because of insurance coverage in my academic center. Then, if there is still persistent SRF or IRF, I will switch drugs. Although studies show that some SRF can be tolerated, I try to treat aggressively in the

beginning to maximally dry the SRF and IRF if possible.[44,50,51,54] If the area improves but there is some residual SRF after switching drugs, I am more tolerant.

Dr Correa: It really depends on how symptomatic the patient is (ie, moderate to severe vision loss) and what the status of the other eye is (normal vision vs worse vision than the eye currently considered for treatment). I think that a key question to ask the patient is, How much is this loss of central vision disruptive to your everyday life?

Dr Talcott: Those are really good pearls—assessing the overall situation beyond just the OCT image in front of us.

Dr Randolph: The key is the newer drugs that may give us longer intervals between injections. Many patients with age-related macular degeneration (AMD) do not drive and are on a fixed income. It is really disruptive for them to come to a clinic. Being able to extend their dosing interval is really important.

Dr Talcott: We are so fortunate to have these medications, especially because of their longer treatment intervals and good drying effect.[21,47] I might consider them as first-line treatments in patients with significant fluid or hemorrhage, given my suspicion that these patients may have a higher initial treatment burden.

Key Takeaways

- Fluorescein angiography and OCT angiography may help distinguish between nAMD and CSR in cases of diagnostic uncertainty
- Consider switching to aflibercept HD or faricimab in cases with persistent fluid after treatment with other anti-VEGF agents
- Consider aflibercept HD or faricimab for patients needing frequent injection intervals
- Considering the patient's symptoms and overall picture is important for treatment selection

Case 2: Persistent Fluid

From the Files of Jessica Randolph, MD

An 83-year-old woman was referred for an AMD evaluation by an outside physician. Visual acuity was 20/60 OU. Examination was significant for normal IOP, pseudophakia, diffuse soft drusen in the macula OU, and exudates OD ***(Figure 5A)****. OCT revealed SRF, exudates, and PED OD* ***(Figure 5B)*** *and drusen OS* ***(Figure 5C)****. Treatment with bevacizumab was initiated OD.*

At the 3-month follow-up after 3 bevacizumab injections, there was residual SRF adjacent to the PED ***(Figure 6A)****. Treatment was changed to aflibercept. Initial improvement was seen, but after 3 injections of aflibercept, fluid worsened* ***(Figure 6B)****. Treatment with aflibercept was continued, with fluctuation in fluid over the following months. At the 1-year follow up, worsening of fluid continued, so treatment was changed back to bevacizumab* ***(Figure 6C)****. At the most recent follow-up, there continues to be persistent fluid* ***(Figure 6D)****.*

"I think that a key question to ask the patient is, How much is this loss of central vision disruptive to your everyday life?"
-Zelia M. Correa, MD, PhD

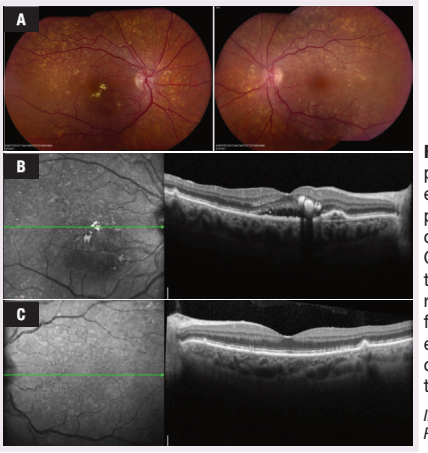

Figure 5. Images of the patient presented in Case 2 at initial examination. (A) Color fundus photography revealed diffuse soft drusen OU and hard exudates OD. (B) Optical coherence tomography image of the right eye revealed subretinal fluid, exudates, and pigment epithelial detachment. (C) Optical coherence tomography image of the left eye revealed drusen.

Images courtesy of Jessica Randolph, MD

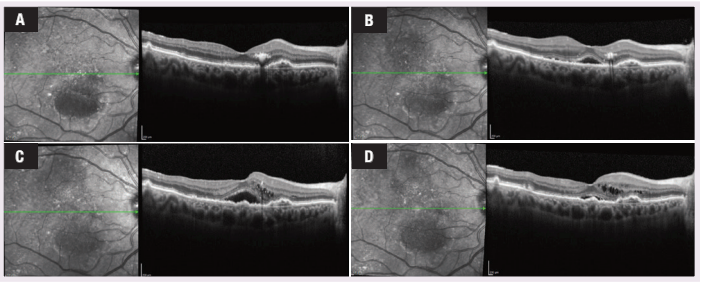

Figure 6. Follow-up optical coherence tomography images of the right eye of the patient in Case 2 after 3 bevacizumab injections (A), 3 aflibercept injections (B), at 1-year follow-up after changing treatment back to bevacizumab (C), and at most recent follow-up after continued treatment with bevacizumab (D)

Images courtesy of Jessica Randolph, MD

"The key is the newer drugs that may give us longer intervals between injections. Many patients with AMD do not drive and are on a fixed income . . . Being able to extend their dosing interval is really important."
–Jessica Randolph, MD

Dr Randolph: At this point, the fluid is stable. Considering the treatment burden for a patient such as this is important. This woman has been coming in monthly for a year, so her daughter has been taking off work and driving her, staying with her for the duration of the visit, and then taking her home. This is a big commitment. The newer medications that have better drying and duration can really help to decrease the caregiver and patient burden. We now have faricimab in the clinic, so that would be an option. Aflibercept HD would also be appropriate because the phase 3 trials showed it results in superior drying compared with aflibercept 2 mg, with more patients experiencing no IRF/SRF.[44]

Is there anything you would have done differently? What are your thoughts on this type of resistant case?

Dr Correa: That is exactly what I would do.

Dr Talcott: These are some of our most challenging cases. These are the patients who I think about switching to other agents, such

as faricimab and aflibercept HD. You have to balance patients' needs and their entire situation, including clinic visits and their impact on the patients' and caregivers' time and QOL.

Dr Correa: Do you ever go back and increase the frequency of injections?

Dr Randolph: I usually start with 4 to 6 weeks. If I see that the patient is unresponsive, then I will cut it back to 28 days exactly and hit it right at 4 weeks.

Dr Talcott: I agree. Many patients whom I started switching to faricimab are already doing 4 to 6 weeks, so I cannot reduce the interval further.

Key Takeaways

- In cases with persistent fluid after treatment with anti-VEGF agents:
  - Consider changing treatment to aflibercept HD or faricimab
  - If using aflibercept 2 mg, bevacizumab, or ranibizumab, consider decreasing the interval between injections to exactly 4 weeks

"…nAMD is not a static disease. The disease and the need for treatment can change with time."
-Katherine Talcott, MD

Case 3: Changing Therapy
From the Files of Zelia M. Correa, MD, PhD

A 72-year-old man with a history of dry AMD OU was referred to the retina clinic by his cataract surgeon after macular changes were noted on preoperative evaluation. On evaluation in the retina clinic, VA was unchanged at 20/50 OU. OCT images revealed drusen OU and a membrane and new SRF OS ***(Figure 7)****. After an initial 1-month observation period, the patient opted to initiate treatment with bevacizumab in the left eye. One month after treatment with bevacizumab, improvement was noted* ***(Figure 8A)****. Six weeks later, however, relapse of fluid and expansion of the membrane was noted* ***(Figure 8B)****. Treatment was changed to aflibercept 2 mg, with good initial response. The patient then underwent cataract surgery. Six months after cataract surgery, OCT image revealed persistent fluid despite continued treatment with aflibercept* ***(Figure 8C)****. Treatment was changed to faricimab. At the next follow-up, the membrane and fluid had resolved* ***(Figure 8D)****.*

Dr Correa: When the patient was receiving aflibercept 2 mg every 4 weeks, he was controlled initially, but then he was not. After treatment with faricimab, the membrane disappeared. At the time, aflibercept HD was not available, so it was a straightforward decision to use faricimab. Because the fluid was increasingly worse, PED developed and the subretinal neovascular membrane had progressed substantially despite the frequent aflibercept injections. It made sense to me to change the medication. After treatment with faricimab, the membrane disappeared.

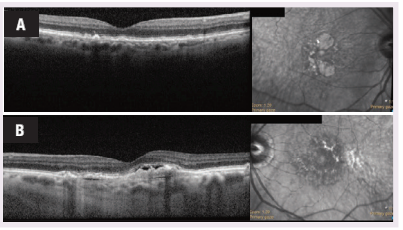

Figure 7. Optical coherence tomography (OCT) imaging of the patient presented in Case 3. (A) OCT image of the right eye showed drusen. (B) OCT image of the left eye showed a membrane and subretinal fluid. Treatment with bevacizumab was initiated.

Images courtesy of Zelia M. Correa, MD, PhD

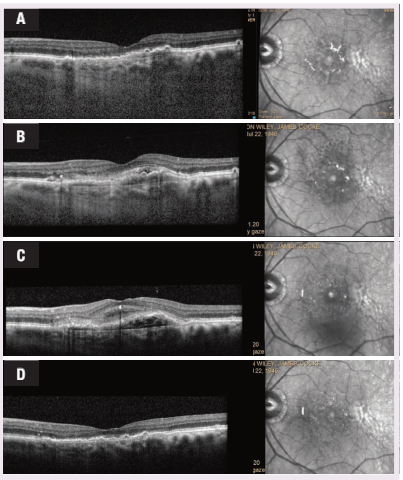

Figure 8. Follow-up optical coherence tomography imaging of the right eye of the patient in Case 3 after initiation of treatment. (A) Initial improvement in fluid after treatment with bevacizumab. (B) Six weeks after treatment with bevacizumab, relapse of fluid and expansion of the membrane was noted. Treatment was changed to aflibercept with an initial good response. (C) Six months after cataract surgery and continued treatment with aflibercept, optical coherence tomography image showed recurrence of fluid. Treatment was changed to faricimab. (D) Follow-up after treatment with faricimab, with resolution of membrane and fluid.

Images courtesy of Zelia M. Correa, MD, PhD

Dr Talcott: This is such a great case. One of the things that I am really struck by with these new, more durable, better drying agents is how they are able to really attack the PEDs.[54] Faricimab, in my experience, has been very good at getting rid of recalcitrant PEDs.[51] This case also really highlights that nAMD is not a static disease. The disease and the need for treatment can change with time.

Key Takeaways

- In patients with an initial good response to treatment with anti-VEGF agents and recurrent fluid, consider changing therapy to agents with a greater drying effect, such as aflibercept HD or faricimab
- The need for treatment can change over time in nAMD

Diabetic Retinopathy/Diabetic Macular Edema: Review of Clinical Trials

Delays in treatment for DR/DME are associated with worse visual outcomes.[56] Even in eyes with good initial VA, a lack of treatment can lead to severe vision loss.[57] Patients with DR are more likely to experience psychological distress, mental illness, and decreased health-related QOL than those with diabetes without eye involvement.[58] In addition, patients with DR/DME are often younger than those with nAMD.[59,60] Thus, vision loss in DR/DME can have consequences for their ability to work, leading to a significant economic impact.[61]

As with nAMD, the first anti-VEGF therapies for DR/DME were administered monthly.[26,62] Bevacizumab has long been used off-label for treatment of DR/DME.[63] Ranibizumab was approved for the treatment of DME in 2012 following the RISE and RIDE phase 3 trials, which demonstrated the efficacy of monthly ranibizumab compared with sham.[64] Ranibizumab was

subsequently approved for the treatment of DR in patients with DME in 2015. Aflibercept 2 mg was approved for the treatment of DME in 2014, with 8-week dosing intervals following an initial monthly loading phase.[65] The VISTA and VIVID phase 3 trials compared aflibercept 2 mg administered every 8 weeks (after a 5-dose monthly loading phase) with macular laser photocoagulation.[66] Patients receiving aflibercept had better VA outcomes than those receiving laser treatment. Aflibercept was subsequently approved for the treatment of DR in 2019.[67] Brolucizumab was approved in 2022 to treat DME following positive results of the KESTREL and KITE studies.[68]

TAE and as-needed dosing protocols have since been studied in patients with DME treated with ranibizumab and aflibercept. Recent meta-analyses revealed similar functional and anatomical outcomes with fixed, TAE, and as-needed approaches, with possibly fewer injections with as-needed regimens.[17,18] As with nAMD, aflibercept HD and faricimab can further extend treatment intervals in DME.

Aflibercept High Dose: PHOTON

Aflibercept HD (8 mg) was approved for the treatment of DR and DME in 2023.[46] The PHOTON phase 3 trial compared aflibercept HD at 12- (n = 328) or 16-week intervals (n = 163) (after 3 monthly doses) with aflibercept 2 mg at 8-week intervals (n = 167) (after 5 monthly doses).[69] Unlike the studies of aflibercept HD in nAMD, not all the patients were treatment naïve.[47] At week 48, 93% of patients maintained a dosing interval ≥ 12 weeks **(Figure 9)**.[69] The mean area of total fluorescein leakage decreased from baseline in all groups (-9.2 for aflibercept 2 mg, -13.9 for aflibercept HD every 12 weeks, and -9.4 for aflibercept 8 mg every 16 weeks). Ultimately, aflibercept HD was approved for a maximum dosing interval of 12 weeks in patients with DR and a maximum of 16 weeks in patients with DME.[47] The safety profile of aflibercept HD was similar to that of aflibercept 2 mg.[70]

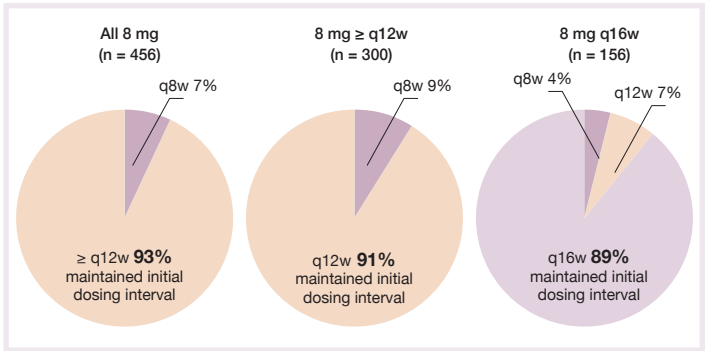

Figure 9. Proportion of patients treated with aflibercept 8 mg with extended dosing intervals at week 48 in the PHOTON phase 3 trial.[69] An interval of at least 12 weeks was maintained by 93% of patients at 48 weeks.

Abbreviations: q8w, every 8 weeks; q12w, every 12 weeks; q16w, every 16 weeks.

Faricimab: YOSEMITE, RHINE, FARETINA-DME

Faricimab was approved for the treatment of DME in 2022, with dosing intervals of up to 16 weeks after an initial 4 monthly injections.[21,71] It currently does not have a specific FDA indication for diabetic retinopathy.[71] The YOSEMITE and RHINE trials compared faricimab with 8-week fixed dosing and TAE dosing for up to 16 weeks with aflibercept 2 mg with an 8-week fixed dosing interval.[72] Noninferiority to aflibercept with respect to VA was demonstrated in both faricimab treatment groups. In addition, more than 70% of patients in the TAE group achieved at least 12-week dosing intervals at year 1 **(Figure 10)**.[72] In both YOSEMITE and RHINE, faricimab achieved greater reductions in CST than aflibercept 2 mg. Faricimab was well tolerated and had a comparable safety profile to that of aflibercept 2 mg.

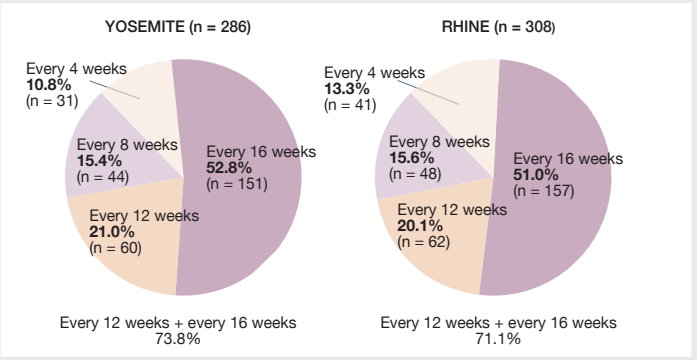

Figure 10. Proportions of patients treated with faricimab with extended dosing intervals in the treat-and-extend group in the YOSEMITE and RHINE phase 3 trials.[72] At 1 year, > 70% of patients achieved an interval of at least 12 weeks.

Reprinted from *The Lancet*, 399, Wykoff CC, Abreu F, Adamis AP, et al, Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials, 741-755, Copyright 2022, with permission from Elsevier.

Similar to the FARETINA-AMD study, FARETINA-DME was a real-world study using Intelligent Research in Sight registry data, including > 2300 eyes treated with faricimab.[73] This included 83% of eyes that were previously treated. After 4 injections, mean change in best-documented VA was 1.0 letter and 4.6 letters for previously treated and treatment-naïve eyes, respectively. After 1 to 2 injections, 60.5% and 67% of eyes in the previously treated and treatment-naïve groups, respectively, achieved extended dosing intervals of > 6 weeks **(Figure 11)**.[73]

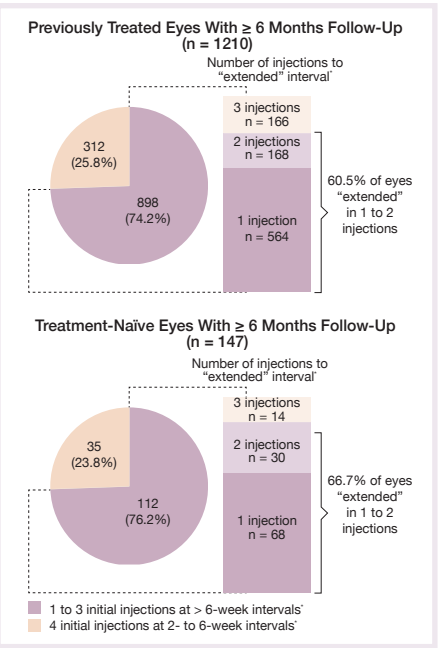

Figure 11. Number of injections before achieving extended injection intervals (> 6 weeks) in the FARETINA-DME study with faricimab for diabetic macular edema.[73] Approximately 60% to 65% of patients achieved extended intervals after 1 to 2 injections.

* Among patient eyes that received ≥ 4 injections. "Extended" interval defined as faricimab injection > 6 weeks after previous faricimab injection.

Case 4: A Patient With DR/DME and a History of Radiation for Choroidal Melanoma

From the Files of Zelia M. Correa, MD, PhD

*A patient with a longstanding history of diabetes presented with a choroidal melanoma in the left eye **(Figure 12)**. His VA was 20/20 OS. On examination by his outside ophthalmologist, the tumor was 2.3 mm in thickness and 16 mm in diameter. At 6 months post radiation treatment, VA was 20/25 OS, and at 12 months, VA was 20/40. At 18 months, he developed cystoid macular edema. The differential diagnosis included DME and radiation retinopathy. Treatment was initiated with bevacizumab by the outside physician. He was then lost to follow-up for 2 years.*

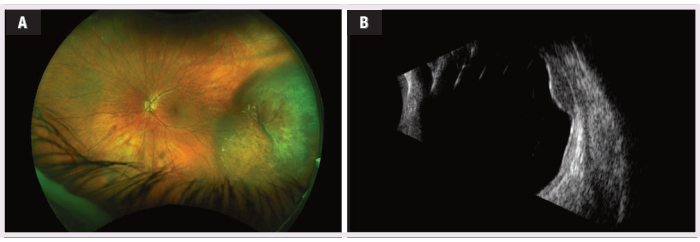

Figure 12. Initial imaging of the patient in Case 4 revealing choroidal melanoma in the left eye on color fundus photography (A) and B-scan (B)

Images courtesy of Zelia M. Correa, MD, PhD

*The patient presented for the first time to the retina clinic at 3 years post radiation treatment. He had been receiving bevacizumab on and off from his outside physician. His VA was 20/200 OS. OCT image revealed IRF and exudates **(Figure 13A)**. Treatment was initiated with aflibercept 2 mg. After 6 months of consistent treatment, there was improvement in the edema, but VA was stable at 20/200 OS **(Figure 13B)**. Examination revealed posterior subcapsular cataract OS, and the patient subsequently underwent cataract surgery. After further monthly aflibercept treatment post cataract surgery, VA had improved to 20/100, but there was persistent fluid **(Figure 13C)**. Treatment was changed to aflibercept HD. The rationale to escalate to aflibercept HD instead of changing the drug was based on the patient's limited improvement but no disease progression. At the next follow-up, VA had improved to 20/80 OS **(Figure 13D)**. Treatment with aflibercept HD was continued every 6 weeks.*

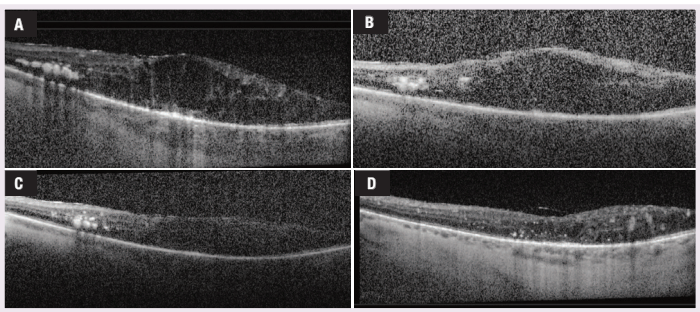

Figure 13. Follow-up optical coherence tomography (OCT) imaging of the left eye of the patient in Case 4 three years post treatment with radiation for melanoma and bevacizumab for cystoid macular edema by an outside physician: (A) initial OCT image revealed intraretinal fluid and exudates; (B) after 6 months of treatment with aflibercept; (C) after cataract surgery and continued treatment with aflibercept with persistent fluid; and (D) after 2 injections of aflibercept high dose every 6 weeks

Images courtesy of Zelia M. Correa, MD, PhD

*At the most recent follow-up, VA was 20/100 OS and 20/20- OD. OCT image of the right eye revealed new IRF **(Figure 14A)**. OCT image of the left eye revealed it was relatively stable, with macular thickening, cotton wool spots, hard exudates, epiretinal membrane, and persistent IRF **(Figure 14B)**.*

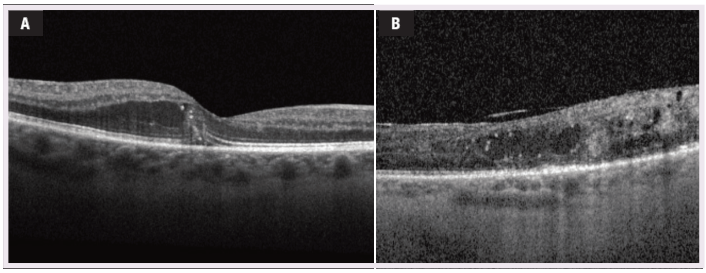

Figure 14. Optical coherence tomography images at the most recent follow-up of the patient in Case 4 after continued treatment with aflibercept high dose in the left eye. (A) Right eye now demonstrates new intraretinal fluid. (B) Left eye is relatively stable with persistent fluid.

Images courtesy of Zelia M. Correa, MD, PhD

Dr Correa: For this patient, the radiation was certainly the trigger but not the only condition responsible for the development of his maculopathy and vision loss in the left eye. This becomes clear now that the right eye is presenting with initial DME. In short, patients with diabetes tend to have more aggressive and harder to control radiation maculopathy.

Would you be aggressive and treat his right eye now?

Dr Randolph: I would wait a little bit. Not necessarily for strictly clinical reasons, but sometimes, it takes the patient a couple of weeks to get comfortable with having injections in both eyes, especially someone like this who has been through a lot already.

Dr Talcott: I agree. You are already going to be keeping close tabs on him for the other eye. This case also highlights how different fluid is from patient to patient, that is, what people notice and what they do not. You really have to treat the patient in front of you and try and tease out what his/her needs are and whether one of the newer agents, such as faricimab or aflibercept HD, is an option.

Dr Correa: I do not even think the DME in the right eye is bothering him that much; although he noticed that something had changed, it is probably more apparent to him because he relies on that eye so intensely.

How much laser are you using for patients with diabetes who have significantly ischemic retinas?

Dr Randolph: I still do a fair amount of panretinal photocoagulation (PRP) because the treatment burden of PRP once or twice per eye vs monthly injections is often preferable.

Dr Correa: I think that PRP really does hold value in DR, especially when you are considering long-term care and access to care.

Dr Talcott: I will often start my patients with proliferative DR with some injections first to calm them down. In some of these patients, I use maintenance anti-VEGF injections to help prevent bleeds.

Key Takeaways

- Consider the patient's symptoms and OCT findings to determine a treatment plan for DR and DME
- Agents such as aflibercept HD or faricimab can be considered to improve VA and fluid in patients resistant to other anti-VEGF therapies
- Consider PRP in patients in whom reduced treatment burden is needed or as an adjunct to anti-VEGF treatment

"With these more durable anti-VEGF agents (such as aflibercept HD and faricimab), hopefully less treatment burden will make it easier for patients to come in."
-Jessica Randolph, MD

Case 5: Treatment Nonadherence
From the Files of Katherine Talcott, MD

*A phakic 43-year-old man with a history of type 2 diabetes on insulin presented to the retina clinic for an evaluation. His last HbA_{1c} was 8.5%. Visual acuity was 20/40 OD and 20/20 OS. OCT image of the right eye revealed IRF and SRF **(Figure 15A)**. OCT image of the left eye demonstrated mild IRF. Treatment with aflibercept 2 mg was initiated OD, with improvement in VA to 20/20 after 3 injections **(Figure 15B)**. The patient was subsequently lost to follow-up for 4 months. At the next follow-up visit, VA had worsened to 20/40 OD, and the fluid had returned **(Figure 15C)**. Aflibercept was administered, with improvement in VA to 20/30 at the next follow-up. Over the following months, the patient was inconsistent with follow-up, with gaps in treatment of 2 to 3 months. Accordingly, there was fluctuation in VA and fluid.*

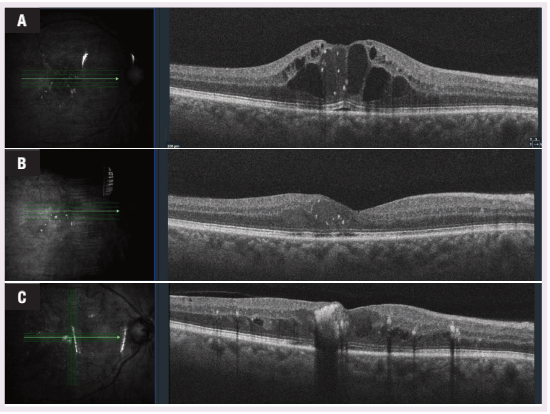

Figure 15. Optical coherence tomography (OCT) imaging of the patient presented in Case 5: (A) Initial OCT image of the right eye; (B) OCT image of the right eye after 3 aflibercept injections; and (C) OCT image of the right eye after the patient was lost to follow-up for 4 months
Images courtesy of Katherine Talcott, MD

Dr Talcott: This is a patient who I feel represents many patients with DR. They have DME, and if I am able to treat them aggressively, they are able to get good vision. Unfortunately, this patient had difficulty making appointments. This is when I think about switching to more durable anti-VEGF agents. One of the potential benefits is to get more time, so if the patient does get lost to follow-up, he/she might not have this fluctuation of fluid.

Would you consider a longer-acting steroid injection in this patient?

Dr Correa: When you have an inflammatory component, patients do really well with an intravitreal steroid.[74] I use the dexamethasone implant in many patients.

Dr Randolph: I have started using steroids a little more quickly than I had previously, especially in patients who have limited response to anti-VEGF injections. There are studies in patients with DME who have had an inadequate response to anti-VEGF therapy that demonstrated a better drying effect with steroids, especially when a steroid implant was used earlier in treatment.[75,76] These studies were done prior to the approval of newer agents such as aflibercept HD and faricimab. With these more durable anti-VEGF agents, hopefully less treatment burden will make it easier for patients to come in.[69,72]

Key Takeaways

- Consider more durable anti-VEGF agents (such as aflibercept HD or faricimab) in patients with DME and inconsistent follow-up
- Consider aflibercept HD in patients treated with aflibercept 2 mg whose dosing intervals have been unable to be extended
- Consider switching to aflibercept HD or faricimab in patients with persistent fluid
- Consider aflibercept HD or faricimab as a first-line treatment in patients with significant fluid or hemorrhage

Case 6: Resistance to Anti–Vascular Endothelial Growth Factor and Steroid Treatments
From the Files of Jessica Randolph, MD

*A 56-year-old woman with a history of type 2 diabetes presented to the retina clinic. Visual acuity was counting fingers OD and 20/70 OS. Intraocular pressure was 22 mm Hg OD and 23 mm Hg OS. On examination, she had early cataracts and severe nonproliferative DR with DME OU. OCT images revealed diffuse intraretinal edema OU and subfoveal lipid OD **(Figures 16A and 16B)**. Treatment with aflibercept 2 mg was initiated, with improvement **(Figures 16C and 16D)**. After 3 injections of aflibercept 2 mg, edema recurred **(Figures 16E and 16F)**, so treatment was changed to the dexamethasone implant. At 1-month follow-up, a good response was noted, but IOP had increased to 29 mm Hg OD and 30 mm Hg OS. Treatment with timolol was initiated. After several months, edema recurred, cataract was noted to be worsening, and IOP had increased.*

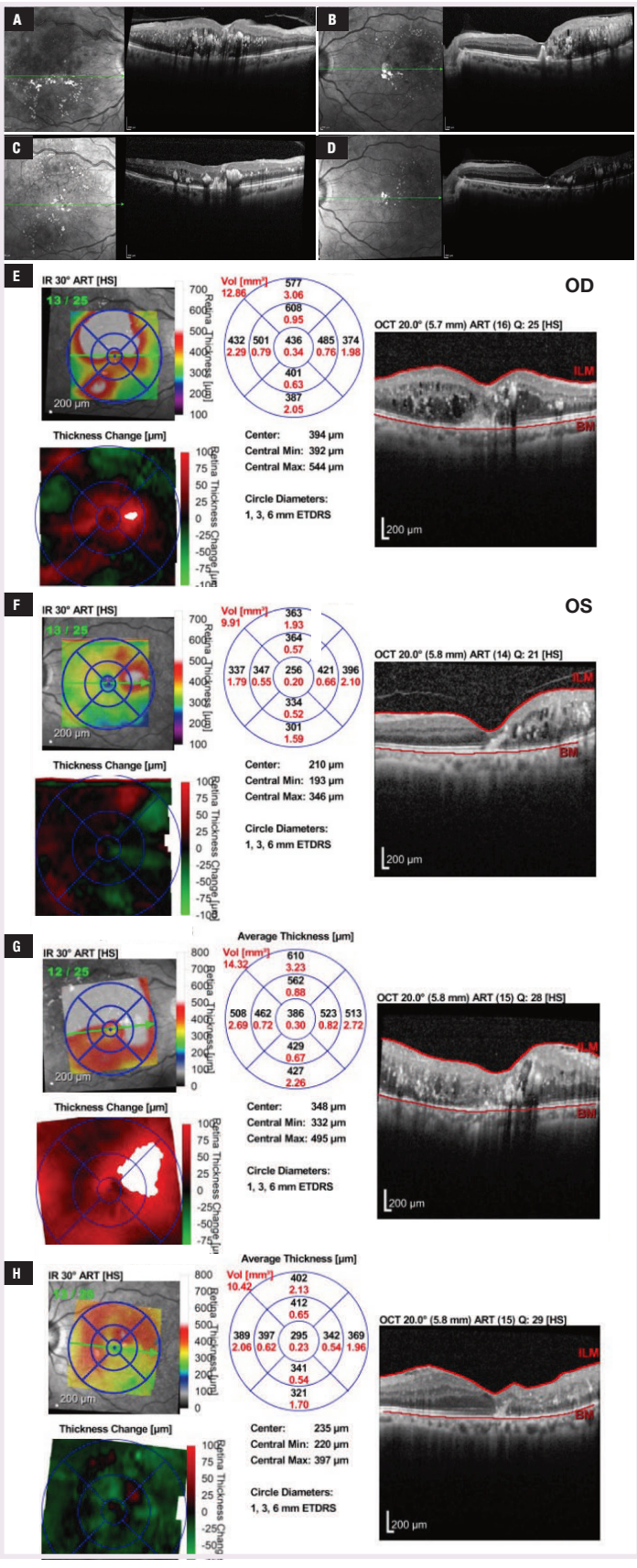

Figure 16. Optical coherence tomography (OCT) imaging of the patient presented in Case 6: Initial OCT images OD (A) and OS (B); OCT images OD (C) and OS (D) after initiation of treatment with aflibercept; OCT images OD (E) and OS (F) after 3 injections of aflibercept, which revealed recurrence of fluid, so treatment was changed to dexamethasone implant; OCT images OD (G) and OS (H) at most recent follow-up

Images courtesy of Jessica Randolph, MD

Treatment for elevated IOP was changed to dorzolamide/timolol. Focal laser was applied OU, and treatment with the dexamethasone implant was continued. Over the following months, the patient underwent cataract surgery and was treated with dexamethasone implant, bevacizumab, and sub-Tenon triamcinolone. At the most recent follow-up, VA was counting fingers OD and 20/50 OS ***(Figures 16G and 16H)****.*

Dr Randolph: For someone such as the patient in this case, I feel that faricimab or aflibercept HD would be a better choice. If I had seen this patient 2 years ago, I certainly would have started one of these 2 agents because she has been really resistant to treatment.

Dr Talcott: What a challenging case! Is there ever a point in which you try to stay away from steroid medications because IOP is creeping up? Do you ever treat with steroid medications with an anti-VEGF agent, going back and forth?

Dr Correa: If the patient is responding to steroid medication, but the IOP is persistently elevated, I will send him/her to the glaucoma specialist and say, "Please use a medical or surgical strategy (with which you feel most comfortable) to ensure IOP control despite the steroid use." Surgical options may vary individually for patients and surgeons. Glaucoma specialists are coming to realize the fine balance between IOP control/prevention of nerve damage and control of macular edema. In cases in which I have to use a dexamethasone implant multiple times, I try to increase the interval between implant insertions and bridge that longer time period with anti-VEGF therapy, which does work.

Dr Talcott: That is a really creative way to bring together different therapies. We are getting to a point now in retina at which we have so many different tools in our toolbox. We have to figure out which tools to use and when in order to optimize patient outcomes.

Key Takeaway

- Consider changing treatment to aflibercept HD or faricimab in patients with poor response to other anti-VEGF or steroid agents or in those with persistent fluid

"We are getting to a point now in retina at which we have so many different tools in our toolbox. We have to figure out how we can integrate everything together."
-Katherine Talcott, MD

DISCUSSION ON COUNSELING WITH THE NEWER AGENTS

"As we start observing the response to these drugs, we are able to be more proactive early on. To me, points to consider are the extent of the nAMD or DME, visual impairment in the worse and in the better eye, patient age, and vision needs."
-Zelia M. Correa, MD, PhD

When a patient comes in and asks for "a 16-week drug", how do you counsel him/her?

Dr Talcott: I first try to discern why he/she is asking for a 16-week drug to elicit the conversation of often burdensome injections. Then, I discuss the newly approved treatments, including faricimab and aflibercept HD, which have shown increased durability, and whether it may benefit the patient to switch.[69,72] I usually set expectations, especially if the patient is someone who needs frequent injections, such as every 4 weeks; then, this is a patient who is unlikely to be able to be extended out to 16 weeks with any drug.

Dr Randolph: I discuss with the patient the new medications, what the indications are, and the risks/benefits. I talk to the patient about the disease process and the pros and cons of switching drugs. Every patient is a little different not only clinically, but socially, so these conversations have to be tailored to the patient.

Dr Correa: I like to start by asking patients why they are "requesting" such treatment and how much do they know about it? Then, I elicit information about their lifestyle, access to office visits, etc, and move on to discuss our options. This conversation does take more than 10 minutes, but it encourages patient autonomy and creates a positive interaction during the treatment decision process.

If you were considering changing agents in a patient who is not meeting treatment goals on his/her current anti-VEGF agent, when would you consider aflibercept HD or faricimab? How would you counsel the patient?

Dr Talcott: It depends on the individual patient. Those I would think about switching are patients with residual fluid or frequent injection intervals. Aflibercept HD might be a good option for patients with some response to aflibercept 2 mg whom I have been unable to extend. Both aflibercept HD and faricimab would be a good consideration for patients with persistent fluid.[69,72] Another point to keep in mind is that aflibercept HD is only approved every 8 weeks after the loading dose. Caution will be needed if the patient is at very frequent intervals, such as every 4 weeks.

Expectations are the biggest factor I address regarding switching. The goals might involve less fluid on OCT images, or being able to go longer with injections. I make sure to mention that these medications are safe and given in the same way as their current medication.

Dr Randolph: This is a question I think we will have better answers to in the future after we have more real-world experience with these 2 drugs. If a patient fails with aflibercept 2 mg, I would be comfortable using aflibercept HD in nAMD or DME. The biggest counseling point, aside from the efficacy data supporting its use, is that it is of a higher volume, so patients may potentially have more IOP spikes afterwards and the sequelae associated with that.[47] For faricimab, the increased viscosity of the medication may create a longer "jellyfish" in the vitreous, so patients may potentially experience that visual phenomenon for longer than with the other drugs. Explaining that when we switch, we will need to start with a loading dose is important, especially for patients who have been able to extend out past monthly injections.

Dr Correa: All the points brought up by both of you are very important. I think retina specialists are currently trying to figure out how to optimize results and achieve stable vision outcomes for their patients. We cannot assume there is going to be a management formula because each individual will have different needs and responses to treatment. That is exactly why we are having this thought-provoking discussion. These new medications offer options and flexible treatment intervals that will benefit patients. I anticipate that as we accumulate more long-term data, our decision tree is likely to become simpler.

Noninjection Strategies to Increase Treatment Intervals and Adherence

Treatment selection in nAMD, DR, and DME must consider each individual patient's characteristics, such as clinical picture, age, medical and social history, and preferences. Particularly for chronic conditions, a shared decision-making process involving the patient in treatment planning has been demonstrated to increase patient satisfaction and reduce nonadherence.[77] Patients with nAMD and DME have identified the physician-patient relationship as an important driver to treatment adherence.[78]

Clear communication between providers and patients is also key. Education on patients' disease process, treatment purpose, and expectations is also important for adherence. Finally, a multidisciplinary care team is often needed for patients with these conditions. To provide optimal care, clear communication among team members (ophthalmologists, optometrists, primary care providers) is needed.

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1. What is your current level of confidence in your knowledge of the most recently approved agents aflibercept HD or faricimab?

   5 = Very confident
   4 = Confident
   3 = Neither confident nor unconfident
   2 = Unconfident
   1 = Very unconfident

2. A 75-year-old woman with a history of AMD presented with blurred vision OS. Visual acuity was 20/20 OD and 20/60 OS. Examination revealed diffuse soft drusen OU and new SRF on OCT image of the left eye. Treatment with monthly bevacizumab was initiated OS. The patient is having difficulty obtaining transportation to the eye clinic and would like to extend the interval between injections. What is the next best step in management?

   A. Continue bevacizumab
   B. Add dexamethasone implant
   C. Switch to faricimab
   D. Initiate TAE with bevacizumab

3. A 64-year-old woman with a history of DR and open-angle glaucoma on dorzolamide/timolol presented for a retina evaluation. Visual acuity was 20/50 OD and 20/20 OS. Intraocular pressure was 20 mm Hg OD and 14 mm Hg OS. The right eye OCT image revealed a small amount of IRF. Treatment with aflibercept 2 mg was initiated OD. After 3 injections of monthly aflibercept, VA was 20/70 OD, with persistent fluid. What is the next best step in management?

   A. Change to aflibercept HD
   B. Continue aflibercept 2 mg
   C. Initiate TAE with aflibercept 2 mg

4. In the pivotal studies PULSAR and PHOTON, patients receiving aflibercept HD were able to extend treatment out to ___ weeks for nAMD, __ weeks for DR, and ___ weeks for DME while maintaining a similar safety profile to that of aflibercept 2 mg.

   A. 8, 12, 16
   B. 16, 12, 16
   C. 18, 12, 16
   D. 16, 18, 24

5. In the real-word studies FARETINA-AMD and FARETINA-DME, > 60% of patients receiving faricimab were able to extend treatment out to ___ weeks for nAMD and ___ weeks for DME while maintaining a similar safety profile to that of shorter treatment intervals.

   A. 4, 4
   B. > 6, > 6
   C. 6, 12
   D. > 12, > 24