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Breaking New Ground

Reducing Treatment Burden in Neovascular AMD

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This continuing medical education activity is provided by **New York Eye and Ear Infirmary of Mount Sinai**.
This educational activity was developed and implemented in collaboration with **MedEdicus LLC**.

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ACTIVITY DESCRIPTION

By 2030, it is estimated that 3.7 million people in the United States will have advanced age-related macular degeneration (AMD), including neovascular AMD (nAMD) and geographic atrophy, yet current treatments for nAMD leave much to be desired in terms of efficacy, safety, and treatment burden. A growing body of research on newly approved or investigational "next-generation" therapies suggests that novel mechanisms of action may lessen treatment burden for nAMD. These include an antibody fragment, a DARPin (designed ankyrin repeat protein), a bispecific antibody, and viral gene delivery and expression. Importantly, no 2 patients are alike in their degree of disease activity and severity, leading experts to question if an individualized approach to treatment with current modalities—along with careful disease activity monitoring—is a viable approach to save vision while reducing treatment burden. This monograph, based on a roundtable discussion among 3 leading retina specialists, will review new developments and cutting-edge data on next-generation treatments and individualized, patient-centered management. A series of challenging cases will also be discussed. The desired results of this educational activity are for retina specialists and other ophthalmologists to evaluate emerging treatments, with the aim to reduce the treatment burden of nAMD while comparing their potential clinical use against the current standard of care.

TARGET AUDIENCE

This educational activity is intended for retina specialists and other ophthalmologists caring for patients with nAMD.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Contrast the mechanism of extended therapeutic effect for investigational and current treatments for nAMD
- Describe recent clinical trial data for approved and emerging treatments for nAMD
- Develop re-treatment plans for patients with nAMD that consider observed disease activity and treatment burden

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Breaking New Ground
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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss in the United States. The number of patients with AMD is projected to grow substantially as the population ages, with a prevalence of more than 3 million projected by 2030 and more than 5 million by 2050.[1] The treatment landscape for neovascular AMD (nAMD) has undergone a period of rapid evolution in the past few years. A variety of investigational agents have demonstrated promising efficacy in late-stage clinical trials, with 1 recent approval of a new anti–vascular endothelial growth factor (VEGF) agent. Some of these investigational and approved agents have encountered safety-related hurdles, yet the strides made in treatment durability are considerable. The art and science of using older approved anti-VEGF treatments according to individual disease activity are also evolving rapidly, leading to better outcomes and reduced treatment burden for patients. This monograph, based on an expert roundtable discussion, will present challenging cases in nAMD along with the latest clinical trial data and perspectives on how the newest advances in nAMD treatment can be translated to the real world.

CASE 1: HARD-TO-TREAT nAMD

From the Files of Arshad M. Khanani, MD, MA

To springboard the discussion, I would like to present a case that highlights some of the most challenging issues we as retina specialists face in treating nAMD. As we move through our discussion, I invite the learners and my co-faculty to reflect on how new and emerging strategies for treating nAMD can be applied to these challenging cases.

–Arshad M. Khanani, MD, MA

Case Presentation

A 75-year-old female presented with a "dark spot in the center" in her right eye. **Figure 1** shows her baseline optical coherence tomography (OCT) images. Her central subfield thickness was 820 µM. Surprisingly, her visual acuity (VA) was still relatively good at 20/50. She received a ranibizumab intravitreal injection (0.5 mg) at that visit and was instructed to follow up in 1 month. When she returned, her retinal thickness had reduced considerably to 470 µM, but fluid had not completely resolved. Her vision had worsened to 20/100. She received another dose of ranibizumab at that visit. After another month, she returned, and her fluid had not changed significantly. Her VA was not tested at that visit because of COVID-19 (coronavirus disease 2019) restrictions. Together, the decision was made to switch from ranibizumab

to aflibercept (2 mg), and she received an injection at that visit. One week later, she followed up to gauge response to aflibercept, and her retinal fluid had almost entirely resolved, and her excess retinal thickness was reduced. Her VA was still declining at 20/150. At her most recent follow-up, approximately 4 weeks after her first injection of aflibercept, fluid had already started to accumulate again, but, encouragingly, her VA had improved to 20/60.

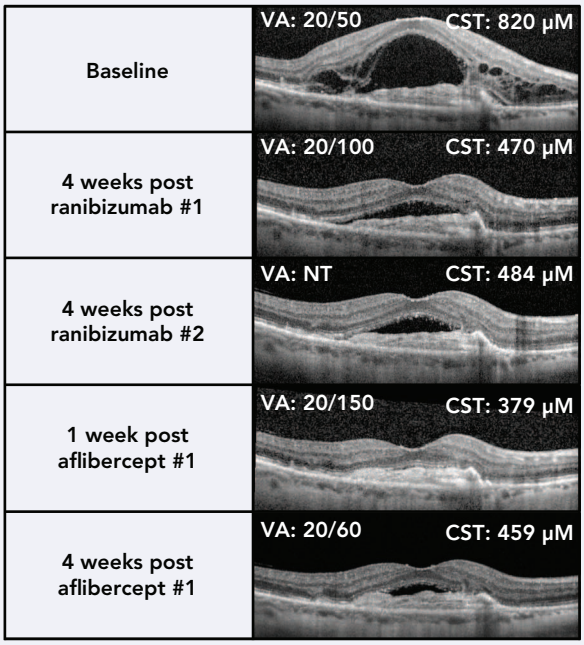

Figure 1. Optical coherence tomography images and visual acuity and central subfield thickness measurements at different treatment timepoints for the patient presented in Case 1

Abbreviations: CST, central subfield thickness; NT, not tested; VA, visual acuity.

Discussion

Dr Khanani: Do you see cases such as this in your practice? Would you have done anything differently?

Dr Kuppermann: I was surprised that her VA was so good at presentation, given that she had such a significant amount of retinal fluid present. Her VA at presentation bodes well for her long-term visual prognosis according to real-world data.[2] Why did you switch anti-VEGF agents after only 2 injections of ranibizumab?

Dr Khanani: The patient expressed dissatisfaction with her VA after receiving ranibizumab, so to meet her treatment goals, we decided to switch to another agent. She had clearly responded, albeit incompletely, to ranibizumab, so another anti-VEGF agent seemed like a rational choice. I counseled her about the efficacy and safety of both aflibercept and brolucizumab, and she decided to try aflibercept.

Dr Weng: A significant proportion of patients respond to anti-VEGF therapy but require frequent injections, sometimes as frequently as every 2 weeks, in the affected eye(s), which poses a tremendous burden on the patient in terms of visit frequency and potential reimbursement issues. In addition, the risk of adverse events increases with each injection, so doubling the injection frequency would in theory double the risk of an adverse event. Such frequent dosing is also off-label, which is a concern.

Dr Khanani: I agree. Treatment burden from frequent visits and injections can lead patients to become nonadherent to their treatment regimen. This has been observed in large studies,[3] and also in my clinic, which serves a large geographic area, with many patients needing to arrange an entire day of travel to see me. Have either of you noticed nonadherence related to limited vision gains?

Dr Kuppermann: I am fortunate that my patient population is very adherent. I have seen, however, that when improvements in vision lag behind improvements in retinal thickness seen on OCT images, that disconnect can lead to nonadherence. I suspect this might have been the case for the patient you presented.

Dr Khanani: I agree. This is a good patient education point that has the potential to encourage adherence to treatment when patients become discouraged about VA improvement after an injection.

Case 1 Take-Home Points

- This case highlights the need for more durable agents that effectively preserve VA and control disease activity
- Shared decision-making regarding treatment can increase satisfaction with treatment, adherence, and, ultimately, visual outcomes
- Improvements in vision can lag behind fluid resolution; patients should be advised that it might take some time for their VA to catch up

UNMET NEEDS IN THE MANAGEMENT OF nAMD

Baruch D. Kuppermann, MD, PhD

Case 1 exemplifies the challenges faced by many retina specialists and their patients, namely, a need for agents and treatment strategies that reduce the frequency of visits and injections required while at the same time preserving vision. Three anti-VEGF agents are now US Food and Drug Administration (FDA) approved for the treatment of nAMD. Although the VA gains across studies have been appreciable (between 6 to 11 letters in the first 2 years), the number of injections required to achieve them remains burdensome **(Table 1)**.[4-11]

Several studies analyzing large populations suggest that in the real world, patients receive only between 4 and 7 injections in their first year of treatment.[12-15] The number of injections received correlates well with visual outcome at 12 months, as seen in multiple clinical trials; not surprisingly, real-world visual outcomes suffer as a result of fewer injections.[3,15] A recent analysis of real-world visual outcomes revealed a steady decline in VA among US patients with nAMD (n = 79,885) treated with anti-VEGF therapies, including ranibizumab, aflibercept, and bevacizumab, over 4 years **(Figure 2)**.[16]

When comparing clinical trial data with real-world outcomes, it is important to remember 2 things: (1) real-world patients are more complex than clinical trial patients; and (2) most retina specialists employ a treat-and-extend (TAE) approach. In the 2018 American Society of Retina Specialists Preferences and Trends (PAT) Survey, 90% of retina specialists reported using TAE,[17] and several studies have shown that it is noninferior to

Table 1. Efficacy and Safety of Approved Anti–Vascular Endothelial Growth Factor Treatments for Neovascular Age-Related Macular Degeneration

Drug	Trial	Dose	Mean BCVA Change at 2 Years, Letters	Safety
Bevacizumab	CATT[4]	1.25 mg every 4 weeks	+7.8	• Higher systemic adverse events with bevacizumab vs ranibizumab
Ranibizumab	ANCHOR/ MARINA[5,6]	0.5 mg every 4 weeks	+6.6 to +10.7	• 1.3%-2.1% endophthalmitis • 6.4%-14.6% ocular inflammation ≥ 1+
Aflibercept	VIEW1/ VIEW2[7]	2 mg every 4 or 8 weeks	+7.6 to +7.9	• Endophthalmitis in < 1%
Brolucizumab	HAWK/ HARRIER[8,9]	6 mg every 12 or 8 weeks	+5.9 to +6.1	• Endophthalmitis < 1% • Inflammation 4.7% • Rare postmarketing reports of vasculitis[10,11]

Abbreviation: BCVA, best-corrected visual acuity.

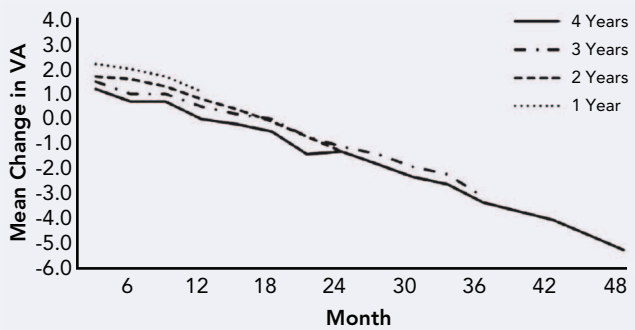

Figure 2. Mean change in visual acuity for eyes with 1 to 4 years of follow-up in the SIERRA-AMD study[16]

Abbreviation: VA, visual acuity.

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monthly or every-8-week treatment.[18-23] In summary, unmet needs in nAMD center around treating retinal fluid in a manner that maintains vision and counseling patients on the importance of keeping a treatment regimen that retains their best VA.

RESEARCH UPDATES AND BEST PRACTICES IN TREAT-AND-EXTEND DOSING

Baruch D. Kuppermann, MD, PhD

The TAE approach has several benefits over fixed or as-needed dosing, including the following:

- Reducing the frequency of visits and injections
- Tailoring treatment to the most detrimental fluid types
- Increasing overall patient satisfaction
- Avoiding undertreatment and associated fluctuations in retinal thickness
- Avoiding overtreatment and the associated risk of geographic atrophy

Patients surveyed about their experiences with treatment of nAMD report significant burdens.[24] These include the direct cost of treatment, indirect costs, and loss of productivity for both

Table 2. Summary of Recent Treat-and-Extend Studies

Study	Extension Criteria	Proportion of Patients on ≥ 12-Week Dosing
TREX-AMD[18] **Ranibizumab (n = 60)**	When macula was dry on spectral-domain OCT, interval extended by 2-week increments	**17%** (2 years)
LUCAS[19] **Ranibizumab (n = 218)** **Bevacizumab (n = 213)**	When no sign of active disease by OCT and biomicroscopic fundus examination, interval extended by 2-week increments	**10%-17%** (2 years)
TREND[20] **Ranibizumab (n = 650)**	When disease activity is resolved by spectral-domain OCT and VA criteria, interval extended by 2-week increments	**22.3%** (1 year)
CANTREAT[21,22] **Ranibizumab (n = 580)**	When VA stably improved, no disease activity, and no fluid on OCT, interval extended by 2-week increments	**29.9%** (1 year)[21] **43.1%** (2 years)[22]
ATLAS[25] **Aflibercept (n = 40)**	When fluid has resolved on OCT, interval extended by 2-week increments	**35%** (1 year) **38%** (2 years)
ALTAIR[23] **Aflibercept (n = 246)**	When no fluid observed on examination, interval extended by 2 or 4 weeks	**58%-60%** (2 years)

Abbreviations: OCT, optical coherence tomography; VA, visual acuity.

patients and unpaid caregivers. Several studies have assessed if TAE dosing can alleviate the burden of frequent injections without sacrificing visual gains **(Table 2)**.[18-23,25] In these studies, visual outcome was similar between the TAE and fixed-dosing arms and also among different anti-VEGF agents. The proportion of patients who were able to be extended to 12-week dosing by the end of each study ranged from 17% to 60%, with more patients extending to 12-week dosing in the second year of study. Extension criteria were similar among the TAE studies; most studies reduced the treatment interval by 2 weeks upon disease recurrence. Notably, in the LUCAS study, investigators observed that patients with disease recurrence during a 12-week interval experienced vision loss even with a 2-week interval reduction.[19] This suggests that either a maximum interval of 10 weeks should be considered with aflibercept or that a more aggressive interval reduction should be considered for patients with disease activity during a 12-week interval.

In the recent SIERRA-AMD real-world study of nAMD treatment and outcomes (n = 79,885), 45.3% and 21.2% of patients achieved 8- and 12-week dosing, respectively.[16] In patients with 4-year follow-up, both VA and injection frequency declined, highlighting the treatment burden and poor VA outcomes in the real world compared with clinical trials.

Fluctuations in retinal thickness (and thereby retinal fluid volume) have gained interest in the past few years as a potential marker for poor long-term visual outcome. In the VIEW1 and VIEW2 (Vascular Endothelial Growth Factor Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration) aflibercept registration trials, a "sawtooth" pattern was observed when plotting the number of patients with retinal fluid or mean retinal thickness over time **(Figure 3)**.[7,26] This pattern of fluid fluctuation has also been observed in the HAWK and HARRIER brolucizumab registration trials and in the CEDAR and SEQUOIA abicipar pegol trials. Specifically, fluctuations were observed in the aflibercept and abicipar pegol arms, respectively.[8,27]

Recently, several post hoc analyses have found a consistent correlation between the magnitude of fluctuation in retinal fluid and long-term visual outcome. When participants in CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) and IVAN (Inhibition of VEGF in Age-Related Choroidal Neovascularization) were grouped by the amount of fluctuation seen in their central retinal thickness (CRT), a strong inverse association was seen with final best-corrected VA (BCVA).[28] Compared with patients in quartile 1 (< 34 μM CRT variation), those in quartile 4 (> 80.6 μM CRT variation) could read 6.27 fewer letters at the conclusion of the study **(Figure 4)**.[28]

Two recent analyses of the HAWK/HARRIER and CEDAR/SEQUOIA data had similar findings, suggesting that CRT fluctuation is not a treatment- or trial-specific phenomenon.[29,30] Interestingly, in the CATT/IVAN post hoc analysis, greater CRT fluctuation was also associated with a heightened risk of developing geographic atrophy,[28] whereas previous studies implicated overtreatment with anti-VEGF agents as a potential causative factor.[4,31,32]

Recognizing the clinical implications of different retinal fluid types can also guide individualized TAE dosing. A growing number of studies suggest that persistent intraretinal fluid (IRF) might be deleterious to long-term visual outcomes, whereas persistent subretinal fluid (SRF) has been associated with more favorable outcomes, including better VA and lower chance of developing geographic atrophy.[33-35] The FLUID study built upon this finding, testing if tolerance of a small amount of SRF (≤ 200 μM at the foveal center) could be used in a TAE strategy, with VA outcomes comparable to those seen with a strategy that prioritizes strict fluid control.[36] At 24 months, the "relaxed" arm (n = 175) demonstrated noninferiority to the "intensive" arm (n = 174), with a mean of 2.6 and 3.0 letters gained from baseline in each group, respectively (P = .99).

To effectively control any type of retinal fluid and prevent the damage associated with large fluctuations, it is imperative to monitor frequently using OCT. Frequent monitoring visits can be a burden to patients and their caregivers, and, in the era of COVID-19, can be associated with elevated risk and anxiety. A device for home OCT monitoring is under investigation, and has the potential to enable patients to reduce their visit burden.[37] In a recent analysis, 90% of users were able to operate the device

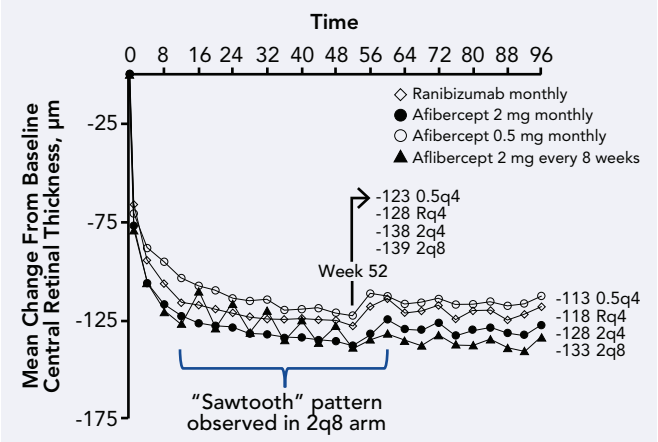

Figure 3. Central retinal thickness over 96 weeks in the VIEW1 and VIEW2 studies[7,26]

Abbreviations: Rq4, 0.5-mg intravitreal ranibizumab every 4 weeks; 0.5q4, 0.5 mg every 4 weeks; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks.

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Primary analysis

FCPT SD	Mean Difference (95% CI)
Quartile 1	0 [Reference]
Quartile 2	-2.68 (-4.71 to -0.64)
Quartile 3	-3.00 (-5.05 to -0.94)
Quartile 4	-6.27 (-8.45 to -4.09)

P value for interaction with trial = .50

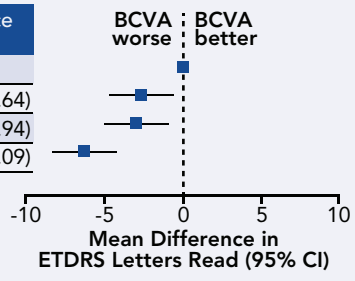

Figure 4. Association between fluctuation in foveal thickness and visual outcome in the CATT and IVAN studies[28]

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; FCPT, foveal center point thickness; SD, standard deviation.

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Table 3. Comparison Between Home Optical Coherence Tomography and Automated Analysis of Retinal Fluid and Investigator Detection of Fluid on In-Office Optical Coherence Tomography[39]

	Investigators	Automated Analyzer
Intraretinal fluid		
Specificity	0.978	0.922
Sensitivity	0.403	0.763
Subretinal fluid		
Specificity	0.973	0.857
Sensitivity	0.583	0.940

after watching a 2-minute tutorial.[38] When the device is used in conjunction with analysis software, the accuracy for detection of IRF and SRF rivals that of practicing retina specialists **(Table 3)**.[39]

Together, these data suggest that after disease activity has been brought under control, an appreciable proportion of patients can be extended in 2-week increments up to every-12-week dosing. Caution should be exercised at longer intervals, with more aggressive interval reduction when fluid recurrence is observed. When IRF is seen, it should be treated right away, whereas small amounts of SRF can be tolerated. Home OCT monitoring has the potential to reduce visit and treatment burden while detecting fluid recurrence at its earliest stages.

Panel Discussion: Current Practices for Treat-and-Extend Dosing

Dr Khanani: Do you use TAE dosing? What proportion of your patients are able to get to every-12-week dosing? In my practice, I estimate that approximately 25% of patients achieve a treatment interval of 12 weeks.

Dr Weng: I use TAE given that it has demonstrated noninferiority in a number of studies.[18-23,25] If optimal VA was the only goal, every patient would be on monthly dosing, but we have to account for the fact that patients simply cannot keep up with that rigorous treatment regimen in the real world. At the beginning of their treatment journey when VA is more steeply rising, patients are generally very adherent, but as seen in the AURA study, adherence often wanes, especially when VA plateaus or when VA goals are not realized.[3]

Dr Kuppermann: In my practice, patients are very adherent, to the point that some of them will choose to remain on monthly or every other month treatment even when I think they may be able to extend. Their fear of vision loss often outweighs the burden of treatment. Has the recent data on fluid fluctuation or fluid types changed how you practice TAE?

Dr Khanani: I still treat with the goal of a dry retina, irrespective of the type of fluid. The fluid fluctuation data are interesting, and it seems that if you have more than 50 µM of fluid fluctuation, visual outcomes begin to be adversely affected. I am interested to see if technologies that deliver a drug continuously to the vitreous result in less fluid fluctuation over time and better VA outcomes.

Dr Weng: I also treat with the goal of a dry retina. I do, however, feel better now about tolerating a small amount of residual SRF that is resistant to frequent treatment if vision is stable, according to what we have observed in post hoc analyses of some very large trials.

Dr Kuppermann: Are either of you using home OCT to monitor fluid?

Dr Weng: I cannot wait for that to become available! It would be a great addition to our practices—if the data continue to be promising—potentially reducing visit burden substantially and allowing a quicker response when fluid does recur.

Dr Khanani: I agree. Home OCT monitoring will be a good addition, especially when used in conjunction with longer-acting therapies or sustained drug delivery technologies.

CURRENT AND EMERGING TREATMENT PARADIGMS FOR nAMD

Christina Y. Weng, MD, MBA

The current gold standard of treatment for nAMD is fixed, frequent dosing of ranibizumab, aflibercept, brolucizumab, or bevacizumab (used off-label for nAMD) **(Table 1)**.[4-9] Brolucizumab is the latest anti-VEGF agent to be approved for use in nAMD, on the basis of data from the phase 3 HAWK and HARRIER trials.[9] It is a small 26-kD humanized antibody fragment able to be delivered at a high molar dose relative to other anti-VEGF therapies **(Figure 5)**.[40,41] In HAWK and HARRIER, patients were randomized to receive either 2 mg of intravitreal aflibercept every 8 weeks, 3 mg of brolucizumab every 8 or 12 weeks, or 6 mg of brolucizumab every 8 or 12 weeks.[8] Participants on every-12-week dosing could be permanently switched to the every-8-week dosing arm if disease activity was observed. Brolucizumab was associated with comparable BCVA gains and better retinal drying at 48 and 96 weeks compared with aflibercept every 8 weeks. Safety was comparable across treatment arms, except for combined intraocular inflammation (IOI), which occurred in 4.7% of brolucizumab-treated patients vs 0.6% of aflibercept-treated patients in HAWK. However, many postmarketing instances of inflammation, including retinal vasculitis and retinal vascular occlusion, have been documented and described.[10,11] These cases continue to be monitored, and a reporting site has been set up by the manufacturer, which, as of August 2020, reports a rate of 10.67 per 10,000 injections.[10] Additionally, a Safety Review Committee was also convened to review these cases; upon review of the phase 3 trial patients, the incident rate of intraocular inflammation was noted to be 4.6% and the overall rate of intraocular inflammation associated with severe vision loss was found to be approximately 1 in 200.

Even with brolucizumab, patients still received between 6 and 8 injections in the first year; although 51% to 56% of patients were able to maintain quarterly dosing through year 1, this measure decreased to 39% to 45% in year 2.[8,42] Similarly, most TAE studies show that less than half of patients are able to achieve ≥ every-12-week dosing **(Table 2)**.[18-23,25] Thus, a treatment option that can be given quarterly or less often while maintaining vision is needed. The following sections will summarize recent research updates on late-stage emerging agents designed to extend the treatment interval further **(Figure 5)**.[40,41,43-46]

Abicipar Pegol

Abicipar pegol (abicipar) is a small, 34-kDa DARPin (designed ankyrin repeat protein) that binds all isoforms of VEGF-A, with high affinity relative to traditional anti-VEGF therapies **(Figure 5)**.[43,47,48] Two double-masked, randomized phase 3 clinical trials, CEDAR and SEQUOIA, compared 2 mg of abicipar, given at fixed-dosing schedules of either every 8 weeks (n = 630)

or every 12 weeks (n = 628), with ranibizumab given monthly (n = 630).[27] The primary outcome was the proportion of patients with stable vision (loss of < 15 Early Treatment Diabetic Retinopathy Study letters) at week 52. A pooled analysis revealed that both dosing regimens of abicipar demonstrated noninferiority to ranibizumab in terms of proportion of patients with stable vision at week 52 **(Figure 6)**.[27] This trend continued in year 2.[49] The ability of abicipar to dry the retina was also similar to that of ranibizumab, but a recently presented preplanned analysis demonstrated that the time to dry retinal fluid was significantly faster with abicipar ($P \leq .006$).[27] Another recent analysis demonstrated that although fluid fluctuation did occur, only 23% to 27% of participants treated with abicipar experienced fluctuations > 50 µM in the first year.[30]

A higher rate of IOI occurred in the abicipar-treated arms (15% in each abicipar arm vs 0.3% in the ranibizumab arm),[27] prompting the FDA to issue a complete response letter indicating that abicipar has an unfavorable benefit-risk ratio in the treatment of nAMD.[50] Before the complete response letter was issued, the manufacturing process of abicipar was modified to enhance the purity of abicipar and to remove potentially inflammatory host-derived contaminants, which reduced the incidence of IOI to 8.9% in the MAPLE study, but these data were not considered by the FDA.[51] The inflammation seen with abicipar was mild/moderate in 75% of cases, and mostly responsive to topical steroids.[52] The manufacturer of abicipar has stated that it is working with the FDA to determine the best next steps for development.[53]

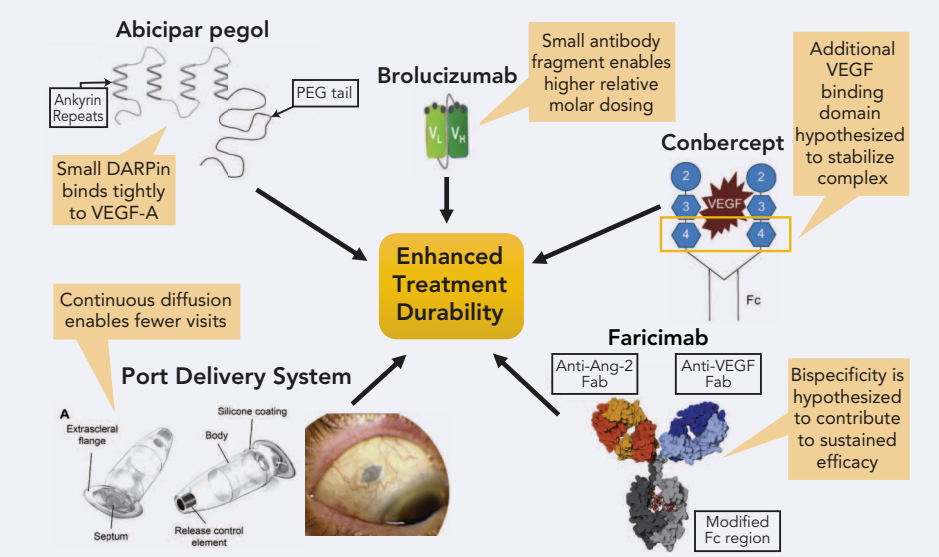

Figure 5. Summary of new and emerging strategies designed to reduce the injection and visit burden associated with treatment of neovascular age-related macular degeneration[40,41,43-46]

Abbreviations: Ang-2, angiopoietin-2; DARPin, designed ankyrin repeat protein; Fab, fragment antigen binding; Fc, fragment crystallizable; PEG, polyethylene glycol; VEGF, vascular endothelial growth factor.

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Conbercept

Conbercept is a fusion protein that is similar to aflibercept, with the addition of an additional immunoglobulin-like VEGF receptor–binding domain that might stabilize the conbercept-VEGF complex **(Figure 5)**.[44] In the phase 3, randomized, sham-controlled PHOENIX study, participants were randomized to receive either conbercept 0.5 mg (n = 81) or sham injection (n = 43).[54] The conbercept arm received 3 monthly injections, then quarterly injections until month 12. The sham arm received 3 monthly sham injections, then at the 3-month primary end point, crossed over to receive 3 monthly conbercept injections followed by quarterly injections until month 12. At the primary end point, mean change in BCVA from baseline was +9.20 letters in the conbercept group and +2.02 letters in the sham group ($P < .001$). At 12 months, BCVA was similar between groups, suggesting there was no significant effect related to the 3-month delay in treatment for the sham group. Compared with

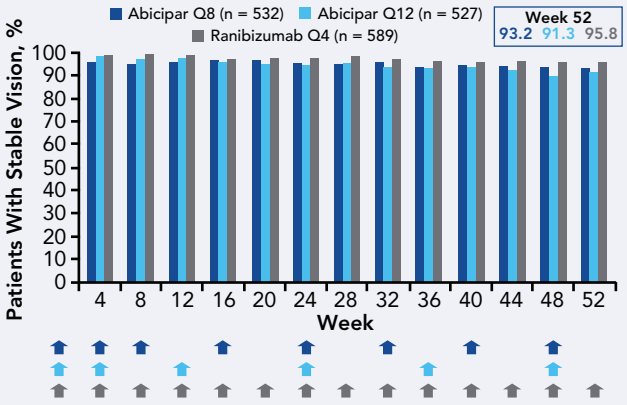

Figure 6. Proportion of participants with stable vision (< 15 Early Treatment Diabetic Retinopathy Study letters loss in best-corrected visual acuity) in a pooled analysis of CEDAR and SEQUOIA.[27] Arrows indicate study drug injection timing.

Abbreviations: Q4, every 4 weeks; Q8, every 8 weeks; Q12, every 12 weeks.

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sham, conbercept was associated with a higher rate of increased intraocular pressure (4.9% vs 0%) and injection site hemorrhage (17.3% vs 2.3%) in months 1 to 3. Conbercept is currently being evaluated in 2 international, 2-year phase 3 trials, PANDA-1 and PANDA-2, in which conbercept 0.5 mg will be given every 8 weeks or conbercept 1.0 mg will be given every 12 weeks and compared against aflibercept 2 mg given every 8 weeks.[55,56]

Faricimab

Faricimab is a bispecific antibody that targets VEGF-A with 1 binding site and angiopoietin-2 with the other **(Figure 5)**.[45] Angiopoetin-2 causes inflammation and vascular destabilization by competing with Ang-1 at the Tie2 receptor.[45] This activity can cause neovascularization and leakage, and simultaneous inhibition of angiopoietin-2 and VEGF has shown an additive benefit in preclinical models of choroidal neovascularization.[45,57] Two phase 2 trials comparing faricimab with ranibizumab, AVENUE and STAIRWAY, have recently completed.[57,58] AVENUE (n = 263) was a 36-week trial intended to assess the efficacy and safety of different doses of faricimab and different dosing strategies compared with ranibizumab 0.5 mg given monthly.[58] The trial did not meet its primary end point of superiority in BCVA at week 36, but the results were nonetheless encouraging and supported pursuing phase 3 trials. In the STAIRWAY trial, participants with treatment-naïve nAMD were randomized to receive either ranibizumab 0.5 mg every 4 weeks (n = 16) or faricimab 6.0 mg every 12 weeks (n = 29) or every 16 weeks (n = 31) following 4 monthly loading doses.[57] The design was similar to that of the HAWK and HARRIER trials in that patients could start the trial at a longer treatment interval and switch to the shorter interval arm if disease activity was observed. The mean change in BCVA was comparable across treatment arms at the 40-week primary end point (+11.4, +9.3, and +12.5 with ranibizumab every 4 weeks, faricimab every 12 weeks, and faricimab every 16 weeks, respectively) and at month 12 **(Figure 7A)**.[57] Anatomic outcomes were also similar **(Figure 7B)**.[57]

The rate of ocular adverse events was similar among groups, and no serious adverse events were observed in any group.[57] One patient in each of the faricimab arms (representing 4.2% of patients receiving treatment every 12 weeks and 3.2% of patients receiving treatment every 16 weeks, respectively) experienced IOI, including mild iritis and mild anterior chamber flare. No patients in the ranibizumab group experienced IOI. Notably, in the faricimab every-16-week dosing arm, 61% of 31 participants demonstrated no disease activity at week 24 and were able to continue every-16-week dosing through the study end. Two phase 3 trials, TENAYA and LUCERNE, are fully enrolled and in progress.[59,60]

Port Delivery System

The port delivery system (PDS) is a refillable implant that is surgically inserted through the pars plana and is anchored in the sclera such that the septum faces outward and the drug reservoir sits in the vitreous cavity **(Figure 5)**.[46] The reservoir is filled with a concentrated formulation of ranibizumab, which elutes in a controlled manner into the vitreous for continuous delivery of a therapeutic level of ranibizumab. In the phase 2 LADDER trial (n = 220), patients receiving PDS 100 mg/mL achieved a median time to refill of 15.8 months **(Figure 8)**, with BCVA gains comparable to those of patients receiving monthly ranibizumab 0.5 mg (5.0 vs 3.9 letters gained at 9 months).[46,61]

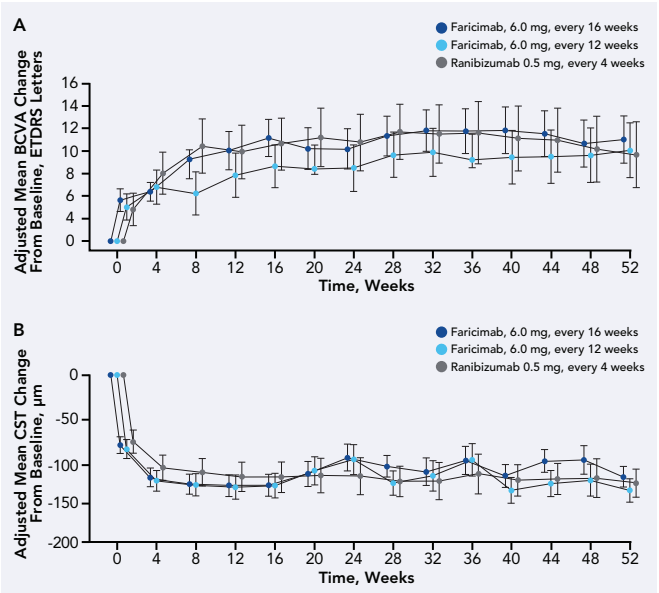

Figure 7. Visual (A) and anatomic (B) outcomes in the STAIRWAY trial comparing faricimab with ranibizumab[57]

Abbreviations: BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

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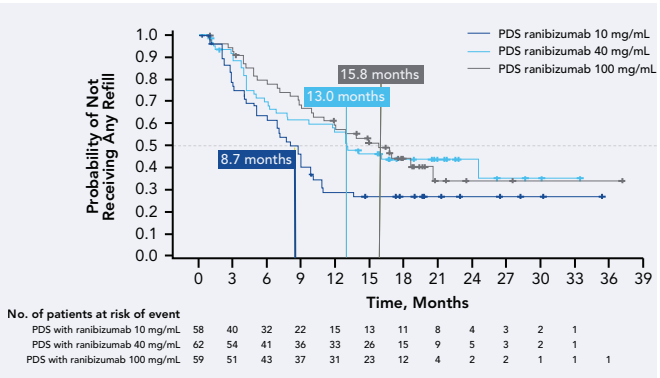

Figure 8. Median time to refill in the port delivery system treatment arms in the LADDER trial[61]

Abbreviation: PDS, port delivery system.

Improvements in retinal thickness were also comparable between the PDS 100 mg/mL and monthly ranibizumab arms.

The most common adverse events were vitreous hemorrhage (50% of all 179 PDS patients) and hyphema (3.4% of all PDS patients).[46] Cataract also developed in a dose-dependent manner (1.7%, 6.5%, and 13.6% in the 10 mg/mL (n = 58), 40 mg/mL (n = 62), and 100 mg/mL (n = 59) groups, respectively). The LADDER trial brought to light several technical challenges related to the implantation procedure for the PDS, prompting protocol improvements that reduced the rate of vitreous hemorrhage to < 5%.

The phase 3 Archway trial is ongoing, and topline data have recently been presented.[62] Patients whose nAMD responded

to anti-VEGF injection were randomized to receive either PDS 100 mg/mL, refilled at week 24 (n = 248), or ranibizumab 0.5 mg given monthly (n = 167). At the 36- to 40-week primary end point, PDS was found to be equivalent and noninferior to ranibizumab monthly injection, with a change in BCVA of +0.2 and +0.5 letters from baseline, respectively. Retinal thickness was similar between the groups. Supplemental ranibizumab injection was permitted in the PDS group, but more than 98% of PDS patients did not require one during the first 24-week interval. The implant was generally well tolerated; however, conjunctival issues arose in 10.9% of participants, and vitreous hemorrhage occurred in 5.2%. As investigators gain experience working in the conjunctival space, several techniques have emerged that are associated with a lower incidence of immediate postoperative adverse events[62,63]:

- Scleral dissection followed by laser ablation of the pars plana
- Conjunctiva and Tenon dissection at peritomy and anchorage of both layers to limbus during closure

Several other treatment strategies that aim to reduce treatment interval are under investigation, including gene therapy, sustained drug delivery systems, and depot drug formulations.[64]

CASES 2 AND 3: FREQUENT INJECTIONS FOR PERSISTENT FLUID

From the Files of Baruch D. Kuppermann, MD, PhD

Case 2

A 76-year-old female presented with new-onset nAMD and a BCVA of 20/50 (20/30 via pinhole occluder). At that visit, she received an intravitreal injection of ranibizumab, and was instructed to follow up in 4 weeks. After 4 weeks, she returned, and OCT examination showed only a small amount of residual fluid remaining **(Figure 9)**. After a series of 4 monthly injections, however, a fair amount of residual fluid had accumulated that appeared to be resistant to ranibizumab treatment. Together with the patient, the decision was made to switch to aflibercept. Four weeks after the patient's first aflibercept injection, the treatment-resistant fluid observed at the last visit had completely resolved.

Case 3

A 91-year-old male who had previously received a series of 3 monthly aflibercept injections was noted to have persistent fluid on OCT images **(Figure 10)**. Six weeks after his fourth aflibercept injection, a small amount of residual fluid still remained. The decision was made to switch to ranibizumab. Five weeks after his first ranibizumab injection, the residual fluid had completely resolved. His VA had also improved from 20/60 to 20/50. His retinal fluid remained controlled with monthly injections of ranibizumab over the next 4 months, and his vision continued to improve.

Discussion

Dr Weng: These cases nicely demonstrate that although we have a wealth of robust clinical trial data available to help guide our decisions, the data describe patients on a population scale. Individuals can have disease that behaves much differently than we might expect; hence, decisions such as when to switch treatments should be individualized.

Dr Khanani: These cases also point to the advantage of having several options available to treat nAMD. Not every patient will respond well to every drug, and it is good that we have a growing armamentarium of therapies to try.

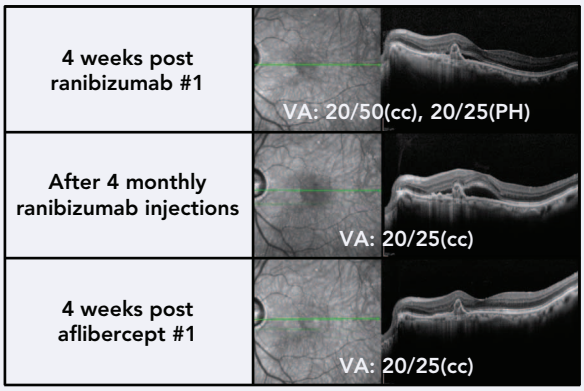

Figure 9. Optical coherence tomography images and visual acuity measurements of the patient in Case 2 at different visits

Abbreviations: PH, pinhole; VA, visual acuity.

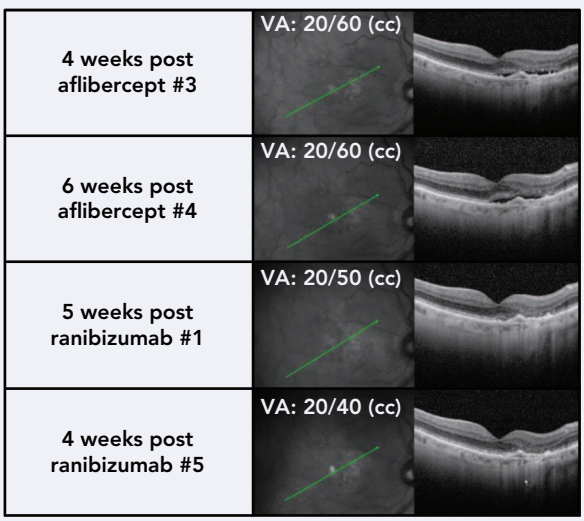

Figure 10. Optical coherence tomography images and visual acuity measurements of the patient in Case 3 at different visits

Abbreviation: VA, visual acuity.

Case Take-Home Points

- Switching anti-VEGF agents in patients who require frequent treatment can be considered
- In contrast to use in diabetic macular edema, the most commonly used anti-VEGF agents can be used in a switching strategy for nAMD, with a generally equal likelihood of success
- Having several options available increases the chances that an agent will be found that works for each patient

CASE 4: TROUBLE ADHERING TO FREQUENT TREATMENTS

From the Files of Christina Y. Weng, MD, MBA

A 71-year-old female with a history of bilateral non-nAMD and cataract presented with new-onset blurry vision in her right eye. Her VA was 20/25 OD and 20/30- OS. She was diagnosed with newly converted nAMD and treated with monthly bevacizumab injections for 3 months. Her retinal fluid resolved nicely **(Figure 11)**, and her vision improved to 20/20- OS, but she mentioned that she had difficulty with the frequent treatment schedule because she is a caretaker for an ill family member. The decision was made to attempt a treatment interval extension to 6 weeks, still using bevacizumab. When the patient returned, a small amount of fluid had recurred, and her VA had dropped to 20/30-. Her interval was decreased back to 4 weeks; her fluid resolved, and she regained 20/25+ vision. A 5-week interval was attempted, but again, her retinal fluid recurred, so her interval was returned to 4 weeks. Although the patient appreciates the visual improvement afforded by strict monthly treatment, she continues to struggle with the logistics of frequent visits, highlighting the pressing need for longer-durability agents.

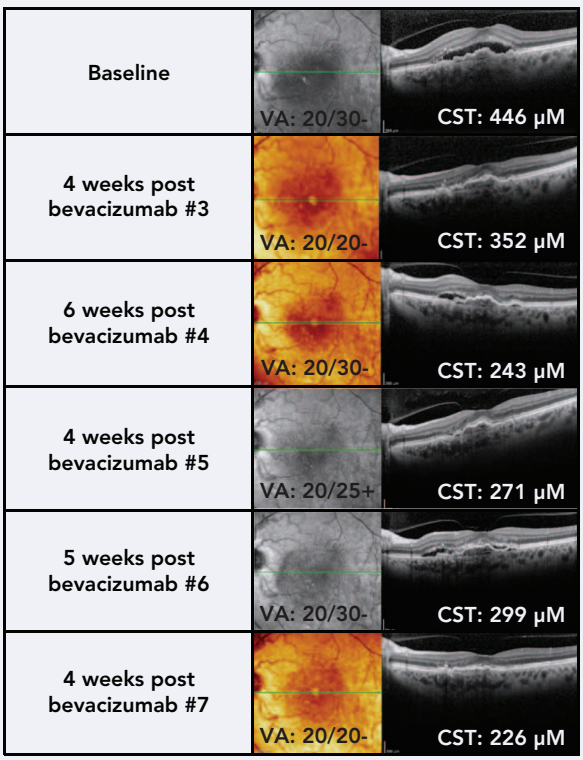

Figure 11. Optical coherence tomography images and visual acuity and central subfield thickness measurements of the patient in Case 4 at different visits

Abbreviations: CST, central subfield thickness; VA, visual acuity.

Discussion

Dr Kuppermann: This is a challenging situation, given that patients would generally prefer a longer treatment interval than that described in this case. Typically, in this setting, I would consider switching to another agent, such as ranibizumab or aflibercept, in the hopes that further extension may be possible. However, there is no doubt that agents with significantly greater durability would be welcome.

Dr Khanani: This case highlights the efficacy of anti-VEGF agents in treating nAMD while acknowledging the limited durability and high treatment burden in some patients. Therefore, we need to look for agents or delivery systems with longer treatment intervals to address this unmet need. These are exciting times in our profession, with so many different options showing promise to address this issue.

Case Take-Home Points

- A substantial proportion of patients with nAMD require strict monthly treatment for optimal disease control
- Real-world challenges make strict monthly treatment unfeasible for many patients
- Chronic undertreatment leads to suboptimal visual outcomes
- Frequent fluctuations in OCT thickness may be detrimental to long-term visual prognosis
- The biggest unmet need in nAMD is durability; we need to continue to look for durable treatment options

Program Take-Home Points

- **A variety of new and emerging treatments for nAMD use innovative molecular mechanisms to extend the duration of therapeutic effect compared with traditional anti-VEGF agents**
- **Recent clinical trial data demonstrate that new and emerging agents are as efficacious as traditional therapies for nAMD, but with a reduced burden of treatment. The quest for a treatment that can be delivered quarterly or less often for most patients is still ongoing.**
- **A growing body of research indicates that TAE dosing is noninferior to fixed dosing. Coupled with individualized, at-home disease monitoring, TAE dosing has the potential to dramatically reduce the burden of visits and treatment for many patients with nAMD.**

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