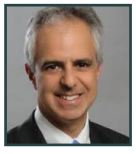
CME MONOGRAPH

IMPROVING TREATMENT BURDEN AND OUTCOMES IN AGE-RELATED MACULAR DEGENERATION

FACULTY



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Neovascular age-related macular degeneration (nAMD) can be successfully treated with long-term monthly or bimonthly anti–vascular endothelial growth factor intravitreal injections. This treatment regimen places a substantial burden on patients that results in noncompliance and subsequent loss of potential visual acuity gains. To address this, treat-and-extend regimens using approved anti–vascular endothelial growth factor agents have been adopted and are described in a growing number of studies. This approach must be highly individualized, however, and monitoring using optical coherence tomography is critical for success. Several emerging therapies with diverse mechanisms to extend durability have entered phase 3 clinical trials. Preliminary data have shown comparable efficacy for several agents, with a reduced injection burden vs the current standard of care. The desired result of this activity is that retina specialists and other ophthalmologists will evaluate emerging treatments for nAMD in the context of the current standard of care for this disease.

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:

- Assess the role of treatment burden on long-term treatment outcomes in patients with nAMD
- Recognize the clinical relevance of clinical trial data on emerging therapies for nAMD
- Develop individualized treatment plans based on evidence-based monitoring strategies for patients with nAMD

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Introduction

By 2030, the prevalence of advanced age-related macular degeneration (AMD), including neovascular AMD (nAMD) and geographic atrophy, is projected to be approximately 3.7 million people in the United States.[1] This growing epidemic will challenge physicians and ocular disease researchers to find new treatment strategies to better meet the needs of patients with this chronic, progressive condition. Treatment of nAMD is not curative, requiring a burdensome treatment regimen to maintain visual acuity (VA), leading many patients to become noncompliant and thus to lose vision. To address this issue, extending the treatment interval with current anti–vascular endothelial growth factor (VEGF) therapies has been used as a strategy; several studies investigating best practices related to "treat-and-extend" (TAE) regimens have shown positive results.

Several new treatment approaches for nAMD are being investigated, with the goal of reducing treatment burden and improving visual acuity gains. This monograph reviews new information presented at a recent continuing medical education symposium on nAMD. Current clinical trial data, expert interpretation of trial design, and real-world cases will be discussed.

Unmet Needs in the Treatment of nAMD

David S. Boyer, MD

Current treatment paradigms for nAMD have shortcomings related to efficacy and treatment burden. Stable increases in VA can be achieved with continuous, fixed-interval anti-VEGF intravitreal injections, as seen in hallmark clinical trials for ranibizumab and aflibercept.[2-4] Unfortunately, several large real-world studies show that dosing in perfect accordance with published trials is unsustainable in clinical practice, with a mean of 4.3 to 6.9 anti-VEGF injections given in the first year of treatment.[5-8] Real-world visual outcomes are also suboptimal. The AURA study was an international retrospective, observational analysis of records from 2227 patients receiving anti-VEGF injections for nAMD over 2 years.[9] Mean VA gains were proportional to the mean number of injections received, but in all countries, initial gains in VA were followed by a gradual decline, in some cases falling below baseline (Figure 1).[9] The primary reasons for treatment discontinuation were stable disease (31.5%) and treatment failure (23.2%). These data suggest that patients might not be aware that adherence to the treatment regimen is needed to achieve and maintain VA gains.

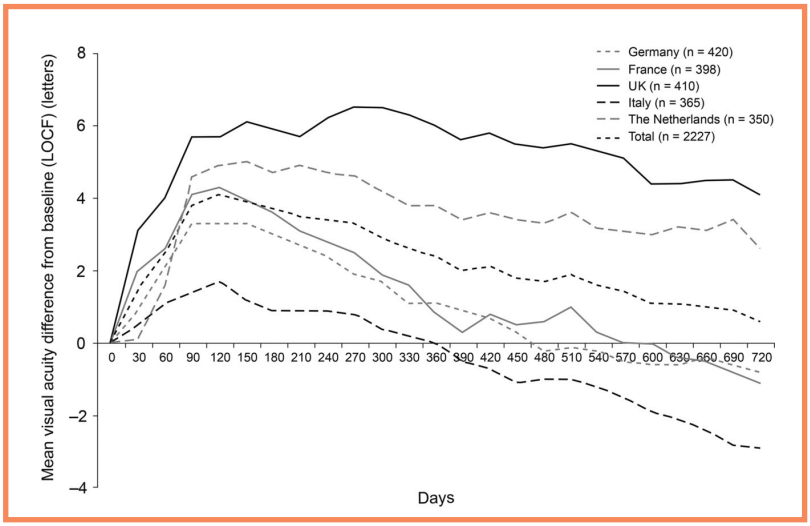

FIGURE 1. Mean change in visual acuity from baseline over time in the AURA study[9]

Abbreviation: LOCF, last observation carried forward.

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To address unmet needs in nAMD, several strategies to reduce treatment burden are being explored. Until new therapies are approved, accumulating data support extending the treatment interval for the anti-VEGF therapies bevacizumab (used off-label), aflibercept, and ranibizumab according to individual assessment of disease activity.[10-13] Emerging strategies to prolong treatment durability include the use of small anti-VEGF molecules with high binding affinity at higher concentrations, modifications to extend half-life or reduce clearance, the use of molecules that target additional angiogenic pathways, and sustained-release devices. Current progress and future directions are discussed in the sections that follow.

Updates on Treat-and-Extend Approaches

Charles C. Wykoff, MD, PhD

To maximize visual outcomes for patients with nAMD using currently available therapies—aflibercept, bevacizumab, and ranibizumab—several strategies are under consideration. First, diagnose and treat patients as early as possible. A large multicenter database study of > 11,000 patients receiving ranibizumab showed that eyes with the worst baseline VA had the best VA gains at 3 months.[14] In terms of absolute VA, however, which relates more closely to function and patient satisfaction, those with the best baseline VA ended the study with the highest VA. These results and those of many other studies confirming such findings underscore the importance of recognizing that change in VA is not equivalent to absolute VA, highlighting the importance of treating while VA is still good. Unfortunately, approximately one-third of patients with nAMD are not diagnosed until their VA reaches approximately 20/70.[15]

Second, avoid undertreatment of active exudative disease. A post hoc analysis of the VIEW 1 and VIEW 2 trials comparing 2 dosing regimens of aflibercept and ranibizumab demonstrated that among patients with persistent subretinal fluid, those who maintained monthly aflibercept dosing (n = 115) achieved a significantly greater VA change from baseline at 52 weeks than patients switched to every-8-week aflibercept dosing (n = 123) (11.7 vs 7.5 ETDRS [Early Treatment Diabetic Retinopathy Study] letters, respectively; *P* = .0006).[16]

Third, apply TAE appropriately. Four notable TAE studies have been published[10-13]:

- TREX-AMD (Treat-and-Extend Protocol in Patients With Wet Age-Related Macular Degeneration)
- LUCAS (Lucentis Compared to Avastin Study)
- TREND (Treat and Extend)
- ATLAS (Aflibercept Treat and Extend for Less Frequent Administration Study)

Two important commonalities among these studies are that the treatment interval was extended only when both subretinal and intraretinal fluid had resolved on optical coherence tomography (OCT)—regardless of VA—and that the interval was extended in 2-week increments only.[10-13] Another important study presented but not yet published is the ALTAIR trial.[17]

TREX-AMD

In TREX-AMD, 47% of eyes receiving ranibizumab in the TAE cohort were at a treatment interval of 8 to 12 weeks at the end of 2 years, with a mean maximum tolerated extension interval of 8.5 weeks.[10] Visual acuity outcomes were comparable in the TAE and monthly-treated cohorts (*P* = .64).

LUCAS

In the LUCAS study—the only TAE trial comparing 2 different medications—441 treatment-naïve patients with nAMD were randomized to receive either ranibizumab or bevacizumab using a TAE protocol.[11] Best-corrected VA (BCVA) in the ranibizumab and bevacizumab groups at 2 years was comparable (6.6 vs 7.4 ETDRS letters, respectively; *P* = .634), but the mean number of treatments given over the study period was significantly less in the ranibizumab group than in the bevacizumab group (16.0 vs 18.2, respectively; *P* ≤ .001), indicating that ranibizumab appeared to have better durability than did bevacizumab.

TREND

The largest TAE study to date is TREND. Treatment-naïve patients in this multicenter international trial were randomized 1:1 to receive ranibizumab on either a TAE regimen (n = 323) or monthly (n = 327).[12] The TAE regimen demonstrated noninferiority to monthly injections (least-squares mean BCVA change of 6.2 vs 8.1 ETDRS letters, respectively; *P* < .0001 for noninferiority). At the end of 1 year, 61.9% of TAE patients were being treated at ≥ 8-week intervals **(Figure 2)**.

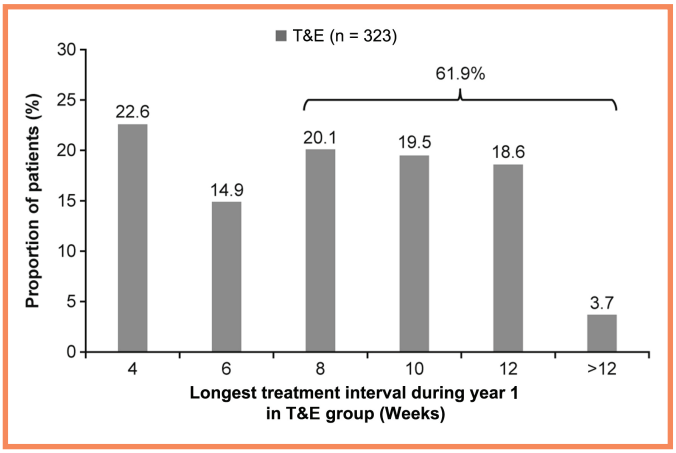

FIGURE 2. Treatment intervals in the TREND (Treat and Extend) ranibizumab study[12]
Abbreviation: T&E, treat and extend.
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ATLAS

In the ATLAS study, 40 treatment-naïve patients in a single arm were treated with aflibercept on a TAE regimen for 2 years.[13] Unlike TREX-AMD, LUCAS, and TREND, each of which had a maximum treatment interval of 12 weeks, the maximum interval between injections in ATLAS was 16 weeks. At 1 and 2 years, the mean letter gain was 7.2 (*P* < .001) and 2.4 (*P* = .269), respectively. The mean number of injections over the study period was 14.5. At the 2-year time point, 38% of patients had a ≥ 12-week treatment interval.

Taken together, the preceding data indicate that we can use the current generation of anti-VEGF monotherapies optimally to better manage nAMD by diagnosing and treating early, aggressively treating persistent fluid, and using OCT and published TAE studies to guide treatment individualization.

Panel Discussion

Dr Wykoff: What do you use to guide the treatment interval when you are using a TAE strategy?

Dr Bakri: I use OCT. In fact, I will check OCT before even checking VA and adjust any decision I have made according to OCT only if there is a sharp drop in VA. Similar to the studies you presented, I typically extend treatment in 2-week intervals, but I sometimes extend the interval by 4 weeks on the basis of encouraging results from the recently presented ALTAIR study, which demonstrated comparable outcomes when extending the treatment interval by 2 or 4 weeks at a time.[17]

Dr Regillo: I extend in 2-week intervals as well, with diligent monitoring by OCT for any fluid recurrence.

Dr Boyer: I use OCT to guide retreatment more than VA, which can vary tremendously, with patients sometimes losing or gaining back several ETDRS letters independent of treatment. It is also important to check vision prior to giving any numbing drops.

Emerging Therapies: Efficacy, Safety, and Treatment Burden

Carl D. Regillo, MD

With the stage set for how best to treat nAMD using the therapies we have today, we can now turn our focus to therapies in the pipeline and how they might address unmet needs, such as better efficacy, better vision outcomes, and reduced treatment burden. Herein, we will review promising new therapies and delivery systems with data from phase 2-and-higher clinical trials.

Brolucizumab

Brolucizumab is a pan-VEGF-A–inhibiting single-chain antibody fragment. It is smaller than other anti-VEGF molecules, and binds with equal affinity as ranibizumab and with higher affinity than bevacizumab.[18,19] Brolucizumab has a much smaller molecular weight (26 kDa) than ranibizumab (48 kDa), aflibercept (115 kDa), or bevacizumab (149 kDa), and it can be dosed at a higher amount (6.0 mg vs 0.5-2.0 mg), which translates into a much higher molar concentration; these attributes, in turn, might contribute to its greater durability of response seen in clinical trials **(Figure 3)**.[18-21]

In a phase 2 clinical trial, brolucizumab dosed every 8 weeks showed comparable efficacy and safety to those of aflibercept dosed every 8 weeks.[19] BCVA remained stable for approximately half the brolucizumab-treated patients whose treatment interval was extended to 12 weeks after week 32. In the phase 3 HAWK and HARRIER trials, patients were randomized to receive brolucizumab 3 or 6 mg every 12 weeks or aflibercept every 8 weeks after 3 loading doses **(Table 1)**.[22-24] Patients in the brolucizumab arms could be switched to every-8-week dosing if disease activity was observed according to protocol-defined changes in VA or intraretinal fluid.[25]

TABLE 1. HAWK and HARRIER Trial Design and Treatment Interval at 48 Weeks[22-24]

Trial	Treatment	Patients Maintained on 12-Week Dosing at 48 Weeks, %
HAWK	Brolucizumab 3 mg (n = 358)	52
	Brolucizumab 6 mg (n = 360)	56
	Aflibercept 2 mg (n = 360)	—
HARRIER	Brolucizumab 6 mg (n = 370)	51
	Aflibercept 2 mg (n = 369)	—

Visual acuity outcomes were comparable across treatment arms, with BCVA changes (least-squares mean) ranging from 6 to 8 ETDRS letters at week 48, demonstrating the noninferiority of brolucizumab.[22] Mean central subfield thickness was significantly lower at 16 and 48 weeks in the brolucizumab 6-mg treatment arm than in the aflibercept arm in both studies ($P = .0016$ and $P < .0001$ at week 16 and $P = .0023$ and $P < .0001$ at week 48 in HAWK and HARRIER, respectively).[26] These results were maintained in year 2 of the study.[27] Additional analyses showed that significantly fewer brolucizumab-treated patients had intraretinal fluid or subretinal fluid at week 96 (24% for brolucizumab 6 mg in HAWK and HARRIER vs 37% for aflibercept in HAWK and 39% in HARRIER; $P = .0001$ and $P < .0001$, respectively).[26,27] Safety was comparable with brolucizumab and aflibercept. The most common ocular adverse events were reduced VA, conjunctival or retinal hemorrhage, vitreous floaters, pain, dry eye, cataract, and vitreous detachment.

Abicipar Pegol

Abicipar pegol (abicipar) is a small (34-kDa) VEGF-antagonizing designed ankyrin repeat protein (DARPin) with higher binding affinity for VEGF than either ranibizumab or bevacizumab.[28] The half-life of abicipar is approximately 2 weeks in human eyes with diabetic macular edema,[29] which suggests that it might have extended treatment durability for nAMD vs traditional anti-VEGF therapies. In the phase 3 CEDAR and SEQUOIA trials, the percentage of patients with stable vision (loss of < 15 ETDRS letters) at 52 weeks was comparable among the treatment arms receiving abicipar 2 mg every 8 weeks, abicipar 2 mg every

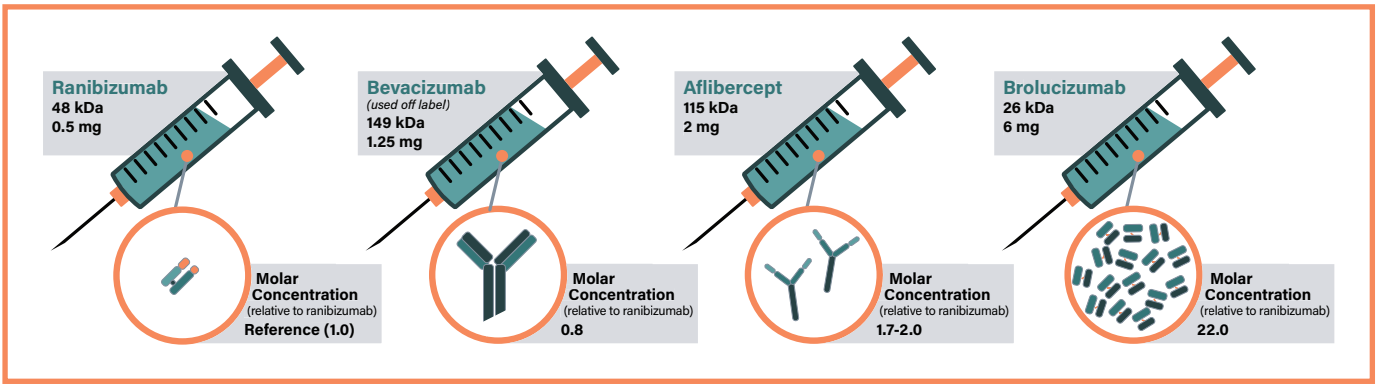

FIGURE 3. Relative concentration of anti–vascular endothelial growth factor drugs in a 0.05-mL injection volume[18-21]

12 weeks, and ranibizumab 0.5 mg every 4 weeks (91%-96%), demonstrating noninferiority for abicipar **(Table 2).**[28]

TABLE 2. Primary Outcome Data in the CEDAR and SEQUOIA Trials[28]

Trial	Treatment	n	Patients With Stable Vision* at Week 52, %
CEDAR	Abicipar 2 mg every 8 weeks	265	91.7
	Abicipar 2 mg every 12 weeks	262	91.2
	Ranibizumab 0.5 mg every 4 weeks	290	95.5
SEQUOIA	Abicipar 2 mg every 8 weeks	267	94.8
	Abicipar 2 mg every 12 weeks	265	91.3
	Ranibizumab 0.5 mg every 4 weeks	299	96.0

* Stable vision defined as a loss of < 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters compared with baseline

Abicipar was also noninferior to ranibizumab for mean change in BCVA. Similar mean central retinal thicknesses were observed among the treatment groups.[28] Ocular adverse events were similar with abicipar and ranibizumab, with the exception of intraocular inflammation, which was observed in approximately 15% of all abicipar-treated eyes vs < 1% of ranibizumab-treated eyes. Trials testing a new formulation of abicipar are currently underway to address this finding.

Conbercept

Conbercept is a human fusion protein similar to aflibercept that incorporates a fourth VEGF receptor-binding domain to potentially extend its half-life.[30] It is approved for use in China[30] and is currently in phase 3 trials in the United States.[31,32] In the phase 3 PHOENIX study conducted in China, patients were randomized to receive either conbercept 0.5 mg (n = 81) or sham injection (n = 43).[30] After 3 monthly loading doses, patients in the conbercept group were maintained on every-12-week dosing for 1 year **(Figure 4).**[30] After 3 months, patients in the sham group crossed over to conbercept 0.5 mg and were given 3 loading doses followed by every-12-week dosing. At the 3-month primary end point, the conbercept group had a significantly better mean change in BCVA than the sham group (9.20 vs 2.02 ETDRS letters; $P < .001$). The conbercept and crossover groups demonstrated similar VA outcomes at 1 year (9.98 vs 8.81 ETDRS letters). Safety was comparable in the conbercept and sham groups at the 3-month time point, with the exception of injection site hemorrhage, which occurred in 17.3% of patients in the conbercept group and in 2.3% of patients in the sham group.

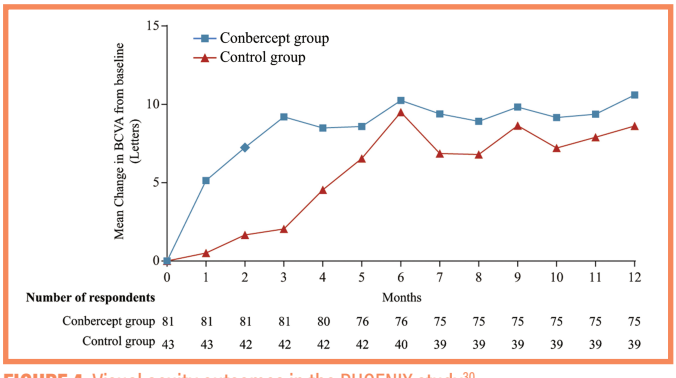

FIGURE 4. Visual acuity outcomes in the PHOENIX study[30]

Abbreviation: BCVA, best-corrected visual acuity.

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Port Delivery System

Another way to achieve treatment durability is to package an anti-VEGF agent into a sustained-release platform. The port delivery system (PDS) is a refillable intraocular reservoir device that is surgically implanted into the pars plana and slowly releases concentrated ranibizumab via passive diffusion into the vitreous. In the phase 2 LADDER trial, 220 patients who had previously demonstrated a response to anti-VEGF treatment were randomized to receive monthly intravitreal ranibizumab 0.5 mg injections or PDS filled with 1 of 3 concentrations of ranibizumab **(Table 3).**[33] The high-concentration ranibizumab PDS (100 mg/mL) performed better than the other 2 doses in a dose-dependent manner. The primary end point of median time to first port refill was 15 months. Mean change in BCVA (ETDRS letters) between randomization and the 9-month time point was comparable with the 100-mg/mL ranibizumab PDS and the monthly ranibizumab injection. Visual acuity remained stable in the high-concentration group through 18 months.[34]

TABLE 3. Phase 2 LADDER Trial of the Ranibizumab Port Delivery System[33]

Treatment	Time to First Required Refill, months	Mean Change in BCVA From Randomization to 9 Months, ETDRS Letters
Ranibizumab PDS 10 mg/mL (n = 58)	8.7	−3.2
Ranibizumab PDS 40 mg/mL (n = 62)	13.0	−0.5
Ranibizumab PDS 100 mg/mL (n = 59)	15.0	+4.3
Ranibizumab 0.5 mg every 4 weeks (n = 41)	—	+3.3

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, port delivery system.

Early in the study, a significant proportion of patients in the PDS groups (28%-60%) experienced vitreous hemorrhage, but improvements in surgical technique have reduced that rate to 4% to 5%.[33] Other adverse events that occurred rarely but more often in the PDS groups included conjunctival erosion, retinal detachment, and endophthalmitis at a rate of 1% to 2%. The phase 3 Archway trial comparing the 100-mg/mL PDS refilled every 6 months with intravitreal monthly ranibizumab is currently recruiting.[35] The primary outcome measure is change in BCVA from baseline to week 40.

Moving Beyond Vascular Endothelial Growth Factor Inhibition

Several other angiogenic pathways are being investigated as potential treatment targets for nAMD, including the complement pathway, angiopoietin, platelet-derived growth factor, integrin, and tissue factor. At present, the most promising investigational therapeutic in this realm is faricimab, a bispecific monoclonal antibody targeting both VEGF and angiopoeitin-2 (Ang-2). Modifications to the Fc region facilitate systemic clearance for improved safety and suppress effector function to enhance treatment durability.[36] Recent phase 2 clinical trial data demonstrate that targeting both VEGF and Ang-2 did not result in increased efficacy vs anti-VEGF therapy alone, but vision and anatomic outcomes were comparable with faricimab dosed every 16 weeks (or 12 weeks if disease activity was observed) and ranibizumab dosed monthly, suggesting enhanced durability with faricimab.[37,38] The safety profile of faricimab was comparable to that of ranibizumab.

Panel Discussion

Dr Regillo: There are quite a few promising investigational treatments in the pipeline for nAMD, with brolucizumab likely to be the first to be approved and commercially available. Treatment burden is expected to be reduced with the agents discussed via extended durability. How will these treatments change your practice if and when they become available?

Dr Boyer: An increased treatment interval for our patients will likely translate to better adherence and better long-term visual outcomes. In the short term, I am eagerly anticipating next steps for brolucizumab. In the long term, I anticipate sustained-delivery systems if the phase 3 clinical trials show good efficacy and safety.

Dr Wykoff: Durability of the current generation of anti-VEGF therapies translates into a substantial treatment burden for patients. Being able to offer approaches that might be able to reduce that burden will be welcomed by patients. I am also hopeful that more consistent and longitudinal anti-VEGF exposure and incorporating additional targets, such as Ang-2, might optimize visual outcomes.

Dr Bakri: Newer agents with extended durability will be a welcome addition for patients. Because brolucizumab is the next agent that may be FDA approved, many patients who cannot be extended on current therapy would likely be switched to brolucizumab in the hopes that better durability can be obtained. We are awaiting the completion of enrollment and results for the phase 3 study of the anti-VEGF (ranibizumab) port delivery device; these results will guide our decision-making as to which patient will be the best candidate for this treatment.

Interpreting the Applicability of Recent Clinical Trial Results to Practice

Sophie J. Bakri, MD

Clinicians naturally strive to find the best possible treatment for patients that results in the best possible outcomes. Given the volume of new clinical trials in nAMD and the complexity of recent study designs, this can be a daunting task. In this section, we will take a critical look at the trial design of several current and emerging treatments for nAMD, focusing on differences in disease assessment and use of comparators. We will also examine the applicability of these trial designs in the real world, and explore how new data can be used to compare emerging agents.

In the phase 3 VIEW 1 and VIEW 2 trials of aflibercept vs ranibizumab, the primary end point was maintenance of vision (defined as a loss of < 3 lines or 15 ETDRS letters).[4] In the first year of the study, participants received either aflibercept (0.5 mg monthly, 2 mg monthly, or 2 mg every 8 weeks after 3 loading doses) or 0.5 mg ranibizumab monthly. This dosing regimen was maintained through the first year. In the second-year extension study, patients were treated on a modified quarterly dosing schedule with retreatment on the basis of changes in fluid, retinal thickness, and vision.[39,40] In the phase 3 HAWK and HARRIER trials, patients were able to maintain quarterly dosing (brolucizumab 3 mg or 6 mg) during the first year of the trial, yielding more usable data on quarterly dosing compared with the VIEW extension trial. This blended study design for brolucizumab is also closer to real life, in that patients could be switched from 12- to 8-week dosing according to the following disease activity criteria assessed at week 16 in HAWK and at several points in HARRIER[24]:

- Decrease in BCVA of ≥ 5 ETDRS letters vs baseline
- Decrease in BCVA of ≥ 3 ETDRS letters and central subfield thickness increase of ≥ 75 µm vs week 12
- Decrease in BCVA of ≥ 5 ETDRS letters due to nAMD disease activity vs week 12
- New or worsening intraretinal cysts or fluid vs week 12

Assessment of disease activity and criteria for retreatment should also be examined carefully when evaluating new clinical trials. Key differences exist among newer studies and hallmark trials of approved agents. For example, in the LADDER trial of ranibizumab PDS, refill criteria were as follows[33]:

- Increase in central foveal thickness ≥ 75 µm vs last 2 visits or ≥ 100 µm vs lowest on-study measurement
- Decrease in BCVA of ≥ 5 ETDRS letters vs average of last 2 visits or of ≥ 10 ETDRS letters vs best on-study measurement
- New macular hemorrhage

In both the PDS and brolucizumab studies, some retinal fluid was tolerated before refill/retreatment. This contrasts with the TREX-AMD, LUCAS, TREND, and ATLAS TAE studies, in which fluid was not tolerated.[10-13] In the as-needed arms of CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) comparing bevacizumab with ranibizumab, fluid, hemorrhage, and unexplained loss of VA in the absence of atrophy or fibrosis were not tolerated.[41,42] The HARBOR trial also had zero tolerance for fluid.[43]

The use of an appropriate comparator agent or control study arm is crucial for evaluating the relative efficacy and safety of treatments for nAMD. In the CEDAR and SEQUOIA trials of abicipar, the every-12-week dosing group received 2 loading doses, whereas the every-8-week group received 3.[28] Otherwise, the study arms were similar, and the efficacy of abicipar and ranibizumab can be directly compared at the 52-week time point. Comparison of brolucizumab and aflibercept in the HAWK and HARRIER trials is a bit more challenging because the first 12 weeks of each study represent the only time the 2 drugs were dosed in a head-to-head manner (Figure 5).[22]

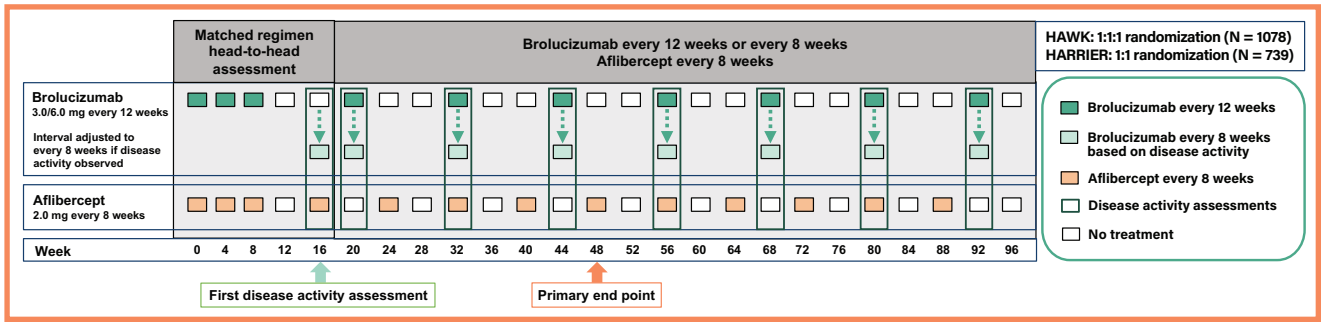

FIGURE 5. HAWK and HARRIER trial designs[22]

Interestingly, in the phase 3 PHOENIX study, conbercept was compared with sham, likely because there was no approved comparator available in China at the time.[30] In the upcoming US phase 3 trials, however, conbercept will be compared with aflibercept, allowing a more direct comparison.[31,32]

Panel Discussion

Dr Bakri: As we have seen, differences in trial design make cross-trial comparison difficult. How do these differing trial designs affect your interpretation of the available data?

Dr Wykoff: It is important to remember that clinical trials are designed to highlight the individual strengths of each investigational agent. We need to take this into consideration when we put the data into a clinical context.

Dr Regillo: We cannot compare trials that do not have identical control arms; for example, this is exactly the case with brolucizumab and abicipar. Until a direct head-to-head comparison is done, it will be hard to know if one treatment is better than another.

Dr Boyer: The tolerance of fluid in some of the studies will likely affect the real-world outcomes we will observe when these agents and delivery systems become available. Because most clinicians do not currently tolerate any fluid, the treatment interval for some of these agents might turn out to be shorter than the data would suggest.

Case 1: Persistent Subretinal Fluid in Neovascular Age-Related Macular Degeneration

From the Files of Sophie J. Bakri, MD

A 79-year-old female was referred for wet AMD. Her VA is 20/70 OD and 20/50 OS. Her right eye also has a cataract and dry AMD. The left eye shows some leakage on fluorescein angiography, a pigmented epithelial detachment (PED), and some subretinal fluid **(Figure 6)**. After 4 monthly bevacizumab injections in the left eye, her VA improved to 20/30, with some subretinal fluid and a low PED remaining. After 4 more bevacizumab injections, her VA improved to 20/25+2. In an attempt to clear remaining fluid, she was switched to monthly aflibercept. The subretinal fluid improved slightly, but some remained. Her VA remained stable at 20/25.

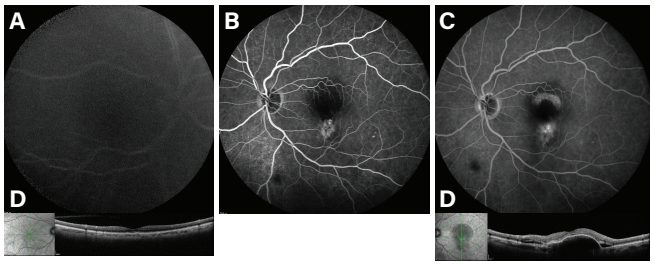

FIGURE 6. (A) Right eye, showing cataract and dry age-related macular degeneration (top) without abnormal fluid (bottom). (B) Early and (C) late fluorescein angiography image of the left eye showing leakage. (D) Optical coherence tomography image of the left eye showing subretinal fluid and a pigment epithelial detachment.

Panel Discussion

Dr Bakri: What would you do in a case such as this, in which there is persistent subretinal fluid with monthly treatment, but vision is acceptable and stable at 20/25?

Dr Wykoff: I would like to continue monthly dosing. However, if the patient desires to attempt a longer interval and understands the risks, I would extend the treatment interval very cautiously, reducing the interval back to monthly dosing if the fluid increases.

Dr Bakri: In the past, I had extended the treatment interval for a patient when fluid was present, and the patient's vision quickly deteriorated to 20/200. I am hesitant to do that again.

Dr Boyer: That has happened to many of us. I think the important point is that in the current generation of clinical trials, some fluid is tolerated. Recent research has even suggested that subretinal fluid in particular might not be as damaging as previously thought, whereas intraretinal fluid might be more closely related to loss of vision.[44]

Dr Regillo: It is also important to note that we do not yet have reliable predictors of response or disease course for nAMD, so individualizing treatment is a trial-and-error process.

CASE 1 TAKE-HOME POINTS

- Fluid might persist even with monthly treatment
- Treating more frequently than every 4 weeks is not feasible
- There is an unmet need for treatments that provide complete resolution of fluid and also reduce treatment burden

Case 2: Using Optical Coherence Tomography to Guide When to Stop Treatment

From the Files of Charles C. Wykoff, MD, PhD

A 67-year-old female is referred for wet AMD in the right eye. Visual acuity was 20/50 at presentation, and 20/25 after 2 years of ranibizumab treatment, with a stable maximum treatment interval of 12 weeks **(Figure 7)**. At the most recent visit, the patient expressed satisfaction with her current VA and asked if she could discontinue injections.

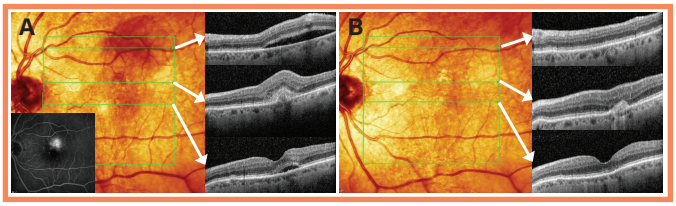

FIGURE 7. Color fundus photographs, fluorescein angiography, and optical coherence tomography images of the right eye of the patient in Case 2 (A) before and (B) after 2 years of treatment with ranibizumab

Panel Discussion

Dr Wykoff: As you can see in the OCT images taken after 2 years of treatment, this patient's fluid has completely resolved. Would you continue every-12-week injections, stop this patient's injections, or consider a longer treatment interval?

Dr Regillo: Having extended treatment for this patient to 12 weeks with the current generation of anti-VEGF treatment and having achieved 20/25 vision is a success. I have not had success with an extension beyond 12 weeks, so I would stay the course.

Dr Bakri: Extending beyond 12 weeks is risky, so I would not.

Dr Wykoff: I agree. It is also important to note that patients at 12-week dosing who have been quiescent can have recurrences, and these should be carefully checked for at each visit. If recurrence is observed on OCT, data from the LUCAS study suggest that the treatment interval should be reduced by > 2 weeks. Patients who had a recurrence while on 6-, 8-, or 10-week treatment intervals maintained vision when the treatment interval was reduced by 2 weeks, whereas patients treated every 12 weeks lost most or all of their VA gains from baseline with a 2-week reduction.[11]

CASE 2 TAKE-HOME POINTS

- Anti-VEGF monotherapies are not a cure for nAMD
- Long-term, consistent treatment has yielded the best outcomes in prospective trials
- Patients treated at longer intervals (ie, > every 8 weeks) should be carefully monitored using OCT
- Any recurrence of fluid should be treated as needed

Case 3: Using Treat-and-Extend in New-Onset Neovascular Age-Related Macular Degeneration

From the Files of Carl D. Regillo, MD

An 84-year-old presented with new-onset nAMD in the right eye. Visual acuity at presentation was 20/400, with blood visible in the center of the macula on the fundus photograph and central foveal neovascularization with leakage evident on fluorescein angiography **(Figure 8)**. The corresponding OCT showed fluid at several levels—intraretinal and subretinal—and even a PED.

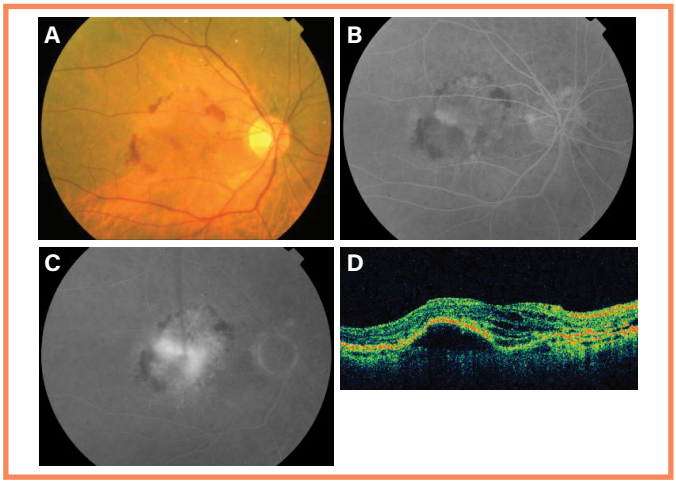

FIGURE 8. Imaging studies done at presentation for the patient in Case 3. (A) Color fundus photograph showing blood at the center of the macula. (B) Early and (C) late fluorescein angiography demonstrating a medium-sized foveal lesion with both classic and occult hyperfluorescence. (D) Optical coherence tomography demonstrating fluid in several retinal layers, including the intraretinal and subretinal layers, and a PED.

The patient was treated with monthly ranibizumab for 2 months, and then started on a TAE regimen once fluid was resolved and VA improved to 20/40 **(Figure 9)**. The patient's treatment interval was extended in 2-week increments. Visual acuity was maintained up to an 8-week treatment interval, but recurrence was observed after the first 10-week interval attempt. Visual acuity was thereafter maintained on an every-8-week treatment dosing interval.

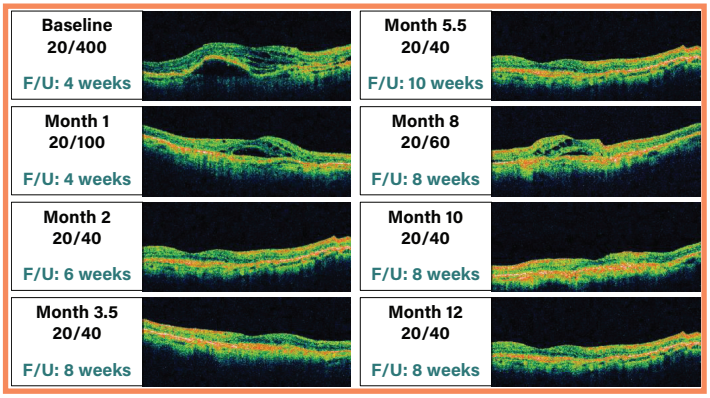

FIGURE 9. Optical coherence tomography of the patient in Case 3 at the time points indicated to the left of the images

Abbreviation: F/U, follow-up interval from indicated visit.

Panel Discussion

Dr Regillo: This case is typical in both presentation and response. I found the disease-free treatment interval to be 8 weeks for this patient, but given the significant burden of treatment long term, I might consider rechallenging the patient again in 3 to 6 months with another treatment extension. If I observe another recurrence, I will stick with 8-week dosing because multiple recurrences over time can lead to some decline in VA. Is this approach consistent with your practice?

Dr Bakri: I agree. This is a classic case of TAE, in which after the maximum interval is found, the TAE paradigm turns into fixed-interval dosing. Every 6 to 12 months, I might try another 1-time extension to see if extending the interval is possible.

Dr Wykoff: Yes, I agree with the management as described. In most cases, I find the maximum tolerated treatment interval to be static over time. In the prospective TREX-AMD trial, a study designed to test the longest tolerated treatment interval over 2 years, 73% of patients were unable to extend their longest tolerated treatment interval when rechallenged, but approximately one-fourth of patients were able to achieve a longer interval upon rechallenge.[10] In practice, I do consider rechallenging the longest tolerated interval when an eye has been stable for multiple cycles.

Dr Boyer: This patient achieved a very good visual outcome and has been able to maintain that improvement over time. Sometimes extending by 1 week can help decrease the treatment burden.

CASE 3 TAKE-HOME POINTS

- It can be reasonable to rechallenge patients with a treatment extension even if they have had a recurrence upon extension in the past
- If a patient has > 1 recurrence on extension, maintain the shorter treatment interval to avoid cumulative damage

Case 4: "I've Noticed Some Distortion."

From the Files of David S. Boyer, MD

A 55-year-old female presented with mild symptoms of metamorphopsia. Her VA was 20/25 OD and 20/40 OS. She had been seen elsewhere by a retina specialist and was

diagnosed with an occult choroidal neovascular membrane and treated with monthly intravitreal bevacizumab in her left eye for 3 months, with no response. She was switched to monthly ranibizumab, again with no response, and finally referred for a second opinion. Upon presentation, drusenoid material and an area of elevation were observed on the fundus photographs (Figure 10). Thinning was observed in the left eye superior and slightly nasal to the fovea, and OCT showed elevation in the macular area of both eyes.

Panel Discussion

Dr Boyer: Would you keep treating this patient? Would you investigate an alternative diagnosis?

Dr Bakri: When a patient does not respond to treatment, I would rethink the diagnosis. In this case, the OCT imaging points to vitelliform dystrophy. Because this can be associated with choroidal neovascularization (CNV), I would recommend additional imaging, such as indocyanine green angiography or OCT-angiography, to rule out CNV. If determined not to be CNV associated, I would then observe without further injections.

Dr Wykoff: This is a fascinating case. I would consider alternative diagnoses, such as vitelliform dystrophy and central serous chorioretinopathy. An indocyanine green angiography and/or OCT-angiography can help confirm the presence or absence of a choroidal neovascular membrane. I would also be interested in the response of the subretinal fluid to an anti-VEGF injection 1 or 2 weeks after the injection. If the fluid is not responsive to anti-VEGF injections and if the patient has not benefited from prior injections, I would consider observing her without continued treatment.

Dr Regillo: I agree. On the basis of the fundus appearance and ancillary imaging, this is likely to be a central vitelliform lesion, which is often misdiagnosed as nAMD, and the lack of any change to a trial of anti-VEGF therapy, along with the retention of relatively good vision, goes along with the diagnosis of a nonexudative vitelliform lesion as opposed to nAMD. OCT-angiography can be used to rule out choroidal neovascularization. I would stop the anti-VEGF injections and observe.

CASE 4 TAKE-HOME POINTS

- When evaluating nonresponse to anti-VEGF therapy in presumed nAMD, possible choices include changing the anti-VEGF agent, shortening the treatment interval, and considering an alternative diagnosis
- Follow up with nonresponders at approximately 2 weeks postinjection to help guide this decision
- An early response to anti-VEGF therapy that is lost by 4 weeks should prompt investigation of alternative diagnoses, such as basal laminar drusen, central serous chorioretinopathy, polypoidal disease, or optic pits, all of which can masquerade as choroidal neovascularization
- When in doubt, perform indocyanine green angiography rather than continuing treatment

Summary and Take-Home Points

- The burden of treatment for nAMD in the real world has now been shown quantitatively through large population-based studies
- Patients are often noncompliant because of a multitude of factors that relate primarily to the required frequency of currently available treatments, resulting in profound loss of initial VA gained from treatment
- To address this pressing public health need, 2 strategies are being explored to reduce treatment burden: (1) developing new drugs and delivery systems with extended durability; and (2) using current therapies in a TAE regimen
- Treat-and-extend regimens can be as effective as monthly or bimonthly treatment, but need to be carefully individualized according to OCT findings at regular monitoring intervals
- Emerging therapies show promise for delivering efficacy that is comparable to established agents, but with fewer treatments

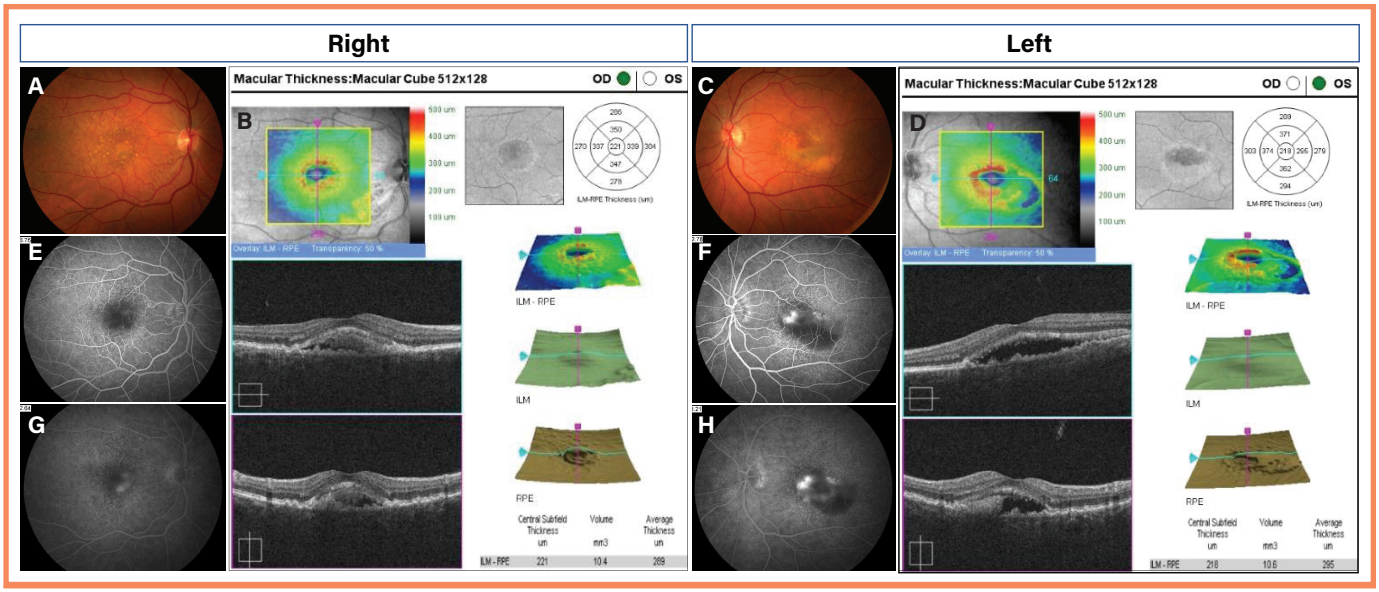

FIGURE 10. Color fundus photographs (A and C), mid fluorescein angiography (E and F), late fluorescein angiography (G and H), and optical coherence tomography (B and D) for the right and left eyes, respectively, of the patient in Case 4

Abbreviations: ILM, internal limiting membrane; RPE, retinal pigment epithelium.

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1. A 75-year-old woman is undergoing anti-VEGF treatment with ranibizumab for nAMD. She has completed 4 months of treatment and has gained 4 ETDRS letters. According to the AURA real-world treatment study, what is the most likely visual outcome for this patient?
   a. Her VA is likely to keep steadily increasing regardless of treatment interval
   b. Her VA gain will be maintained regardless of treatment interval
   c. Her VA gain is likely to decline unless she continues monthly treatment
   d. Her VA is likely to plateau with continued monthly treatment

2. By which mechanism is brolucizumab theorized to increase the durability of response vs traditional anti-VEGF agents?
   a. Higher molar concentration
   b. Targeting the angiopoietin pathway
   c. Continuous drug delivery
   d. Targeting multiple pathways

3. By which mechanism is faricimab theorized to increase the durability of response vs traditional anti-VEGF agents?
   a. Extended half-life
   b. Targeting additional VEGF-binding domains
   c. Targeting multiple pathways
   d. Continuous drug delivery

4. Which of the following describes a key result from the CEDAR and SEQUOIA trials of abicipar?
   a. More than half the patients treated with abicipar were maintained on 12-week dosing at 1 year
   b. > 90% of patients treated with abicipar maintained stable vision through 1 year
   c. Mean BCVA gains were comparable in the abicipar and aflibercept arms
   d. Mean central retinal thickness was significantly lower with abicipar than with ranibizumab at 1 year

5. It is difficult to directly compare drugs across different clinical trials because of:
   a. Differences in the control arm(s)
   b. Differences in retreatment criteria
   c. Different definitions of disease activity
   d. All the above

6. A 78-year-old male treated with monthly ranibizumab for nAMD for 4 months reports difficulty arranging travel and would like to skip his next scheduled injection. Currently, his VA is 20/30 and his central retinal thickness was reduced by 80% from baseline, with a small amount of subretinal fluid remaining. According to recent TAE studies in AMD, when can the interval of treatment for this patient be safely extended?
   a. After 4 months of continuous anti-VEGF treatment
   b. After 1 year of continuous anti-VEGF treatment
   c. Once all neovascularization has resolved
   d. Once subretinal fluid has resolved

7. A patient who has been maintained successfully on every-12-week dosing of aflibercept develops a recurrence of fluid, with slightly reduced VA. According to the LUCAS study, which is the best treatment strategy for this patient?
   a. Continue every-12-week dosing
   b. Reduce the treatment interval by 2 weeks
   c. Reduce the treatment interval by 4 weeks
   d. Switch to a different anti-VEGF treatment