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LEARNING METHOD AND MEDIUM
This educational activity consists of a supplement and ten (10) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

ACTIVITY DESCRIPTION
By 2030, it is estimated that 3.7 million people in the United States will have advanced age-related macular degeneration, including neovascular age-related macular degeneration (nAMD) and geographic atrophy. Current treatments for nAMD leave much to be desired in terms of efficacy and treatment burden. New and emerging treatments for nAMD use novel molecules, delivery modalities, and targets to achieve better treatment longevity and reduced treatment burden. These include a DARPin (designed ankyrin repeat protein) (abicipar pegol), a small anti–vascular endothelial growth factor (VEGF) monoclonal antibody fragment (brolucizumab), an implantable delivery system (ranibizumab port delivery), and a monoclonal antibody with multiple angiogenic targets (faricimab). Vision maintenance, change in best-corrected visual acuity, and retinal fluid resolution are among the end points being explored vs traditional anti-VEGF agents in phase 2 and 3 clinical trials, with promising results. Developing retreatment plans for patients should balance fluid resolution and injection burden, considering a treat-and-extend approach. This activity captures the proceedings of a live roundtable discussion of expert retina specialists held during the AAO2020, Exudation, and Degeneration 2020 meeting. The desired results of this educational activity are for retina specialists and other ophthalmologists to evaluate emerging treatment strategies for nAMD in the context of 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:
- Describe the mechanism of extended therapeutic effect for investigational treatments for nAMD
- Discuss clinical trial data for approved and emerging treatments for nAMD
- Develop retreatment plans for patients with nAMD guided by recent clinical trial results

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THERAPEUTIC LANDSCAPE FOR nAMD

Age–related macular degeneration (AMD) is the leading cause of blindness in developed regions of the world, and accounts for nearly 9% of all blindness worldwide.\(^1\) In 2020, approximately 196 million people are affected with AMD worldwide; this number is projected to grow to 288 million by 2040.\(^2\) The disease begins as dry—or nonneovascular—AMD, and, in some eyes, progresses to wet—or neovascular—AMD (nAMD). Vision loss can occur in eyes with advanced dry AMD (primarily from geographic atrophy involving the fovea), but most AMD–related vision loss arises from the development of choroidal neovascularization (CNV) associated with nAMD.\(^3\) nAMD accounts for only 10% to 15% of all AMD, but is responsible for more than 80% of all AMD–related vision loss.\(^5\)

Three inhibitors of vascular endothelial growth factor (VEGF)—ranibizumab, aflibercept, and brolucizumab—are approved by the US Food and Drug Administration (FDA) for the treatment of nAMD, and a fourth drug—bevacizumab—is often used off-label because of its cost advantage over the 3 indicated products. The efficacy and safety profiles of these drugs have been established in well–designed and appropriately powered phase 3 trials, and the safety of brolucizumab continues to be evaluated as real–world use expands.\(^4\) They are associated with significant treatment burden, however, requiring regular repeated injections every 1 to 3 months according to their labels. In the real world, these drugs are associated with a high injection frequency to maintain vision.\(^5\)

Ranibizumab was compared with sham injection in MARINA (Minimally Classic/Occult Trial of the Anti–VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and with photodynamic therapy (PDT) with verteporfin in the ANCHOR (Anti–VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) study.\(^6,7\) In MARINA, ranibizumab 0.3 mg (n = 238) and 0.5 mg (n = 240) administered by monthly intravitreal injection maintained best–corrected visual acuity (BCVA) better than did sham therapy (n = 238), with 92%, 90%, and 53% of eyes, respectively, losing < 15 letters of BCVA at 24 months (P < .001 for each ranibizumab dose vs sham).\(^8\) In ANCHOR, 90%, 90%, and 66% of eyes receiving ranibizumab 0.3 mg (n = 140), ranibizumab 0.5 mg (n = 140), or PDT (n = 143), respectively, attained the same primary end point (P < .0001 for each ranibizumab dose vs PDT).\(^9\) Low rates of endophthalmitis—less than 1%—were seen in these trials and were attributed to the injection procedure rather than the drug. Other uncommon serious ocular adverse events included low–grade inflammation, retinal detachments, and vitreous hemorrhages.\(^5\) Ranibizumab was also compared with off–label bevacizumab in CATT (Comparison of Age–Related Macular Degeneration Treatments Trials), which demonstrated comparable BCVA outcomes at 2 years,\(^8\) superior BCVA outcomes with monthly vs as–needed injections,\(^8\) superior fluid resolution with ranibizumab vs bevacizumab, and comparable ocular safety of the 2 agents.\(^8\)

Aflibercept was compared with ranibizumab in the VIEW 1 and VIEW 2 (Vascular Endothelial Growth Factor Trap–Eye: Investigation of Efficacy and Safety in Wet Age–Related Macular Degeneration) studies.\(^10\) In VIEW 1, < 15 letters of BCVA at 12 months (the primary end point of the VIEW 1 and VIEW 2 studies) was lost by 95% of 301 patients receiving aflibercept 0.5 mg every 4 weeks, by 95% of 304 patients receiving aflibercept 2 mg every 4 weeks, by 94% of 301 patients receiving aflibercept 2 mg every 8 weeks, and by 94% of 304 patients receiving ranibizumab 0.5 mg every 4 weeks. In VIEW 2, the primary end point was attained by 95% of 296 patients receiving aflibercept 0.5 mg every 4 weeks, by 95% of 309 patients receiving aflibercept 0.5 mg every 4 weeks, by 95% of 306 patients receiving aflibercept 2 mg every 8 weeks, and by 95% of 291 patients receiving ranibizumab 0.5 mg every 4 weeks. In both studies, all doses of aflibercept were noninferior to ranibizumab for this primary end point. Aflibercept 2 mg every 4 weeks more effectively dried the macula, and eyes with early persistent fluid had better BCVA outcomes with every–4–week dosing than with every–8–week dosing.\(^11\) The safety profiles of all 4 treatments were similar; serious ocular adverse events were uncommon and included endophthalmitis, reduced visual acuity (VA), and retinal hemorrhage.\(^10\) Arterial thromboembolic events were rare and had a comparable incidence among the groups.\(^10\)
Brolucizumab, an antibody fragment, is the most recently approved drug for nAMD. This newly approved agent was designed to confer a reduced treatment frequency compared with the other anti–VEGF agents. It is thought to achieve a prolonged duration of activity given its small size and higher molar dose compared with aflibercept, bevacizumab, or ranibizumab. The phase 3 HAWK and HARRIER trials compared brolucizumab 3 mg every 12 weeks (n = 358; HAWK only), brolucizumab 6 mg every 12 weeks (n = 360 in HAWK; n = 370 in HARRIER), and aflibercept 2 mg every 8 weeks, the FDA-approved dose at the time of the study (n = 360 in HAWK; n = 369 in HARRIER). As part of a flexible trial model, the brolucizumab dosing interval was reduced to every 8 weeks if disease activity was observed at week 16 and at each assessment thereafter in the every-12-week arm of the study.9 The primary efficacy outcome was change from baseline in mean BCVA at 12 months in HAWK, mean BCVA changes from baseline were +6.1 letters, +6.6 letters, and +6.8 letters with brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept, respectively, with both brolucizumab groups being noninferior to the aflibercept group. In HARRIER, the mean BCVA change from baseline with brolucizumab 6 mg (+6.9 letters) was also noninferior to that seen with aflibercept (+7.6 letters). Overall, 51% to 56% of eyes receiving brolucizumab 6 mg every 12 weeks were maintained with every-12-week dosing through 12 months in these 2 trials. In both studies, fewer eyes receiving brolucizumab 6 mg had any subretinal and/or intraretinal fluid on optical coherence tomography (OCT) images at months 4 and 12 compared with eyes receiving aflibercept (relative risk reductions of approximately 30%–50%; P < .001 across studies and time points), and mean central subfield thickness was lower at month 12 in eyes receiving brolucizumab than in eyes receiving aflibercept (P < .001).

A recent 24-month analysis from these studies confirmed the durability of these findings through 2 years of treatment, although by the end of month 24, only 45% of 360 HAWK patients and 39% of 370 HARRIER patients on brolucizumab 6 mg were still maintained on every-12-week retreatment (Figure 1).12,14 The most common adverse events associated with brolucizumab are blurred vision (10%), cataract (7%), conjunctival hemorrhage (6%), vitreous floaters (5%), eye pain (5%), and intraocular inflammation (4%).15 Postmarketing cases of retinal vasculitis and retinal vascular occlusion have occurred, prompting the manufacturer to launch an adverse event reporting site to collect and share pertinent data.4

**CURRENT nAMD TREATMENT BURDEN IS UNSUSTAINABLE**

The clinical trials described previously,6-12,15 coupled with many others,16-21 convincingly demonstrate that consistent anti–VEGF dosing at a regular interval—eg, every 1, 2, or 3 months—produces others,16-21 convincingly demonstrate that consistent anti-VEGF therapies when its effect begins to wane.8,22 More than those achieved with irregular administration of as-needed dosing at a regular interval—eg, every 1, 2, or 3 months—produces others,16-21 convincingly demonstrate that consistent anti-VEGF.

With investigator-driven injection frequency phase.24 More broadly, a comparison of first-year injection rates in randomized clinical trials compared with real-world studies (Figure 3) demonstrates the extent to which anti-VEGF therapy is underdosed in clinical practice, at the cost of smaller visual gains.5,7,10-12,25

**Figure 1.** Best-corrected visual acuity changes from baseline in the HAWK and HARRIER phase 3 clinical trials of brolucizumab13,14

*Noninferiority margin = 4 letters

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LS, least squares; SE, standard error.

Permission request submitted.
REDUCING nAMD TREATMENT BURDEN: HOME OCT AND TREAT-AND-EXTEND ANTI-VEGF DOSING STRATEGY

The current approach to nAMD monitoring and therapy is costly and, as demonstrated previously, suboptimally effective in the real-world setting. There is a significant unmet need for more efficient monitoring and treatment strategies that reduce the burden of nAMD management.

Improved home monitoring for patients with AMD has the potential to both reduce the frequency of office visits for disease activity assessment and detect conversion to nAMD earlier than by traditional means. Early detection is crucial for preserving VA because baseline VA is a powerful predictor of final VA in eyes with new-onset nAMD receiving anti-VEGF therapy.26,27 A patient-operated home OCT device (Notal Vision) is in development; it has demonstrated a sensitivity of 91.5% and a specificity of 97% vs conventional OCT operated by trained personnel in detecting intraretinal and/or subretinal fluid in the macula of eyes with new-onset nAMD.28 In a study of 347 eyes of 196 patients with intermediate AMD, an average age of 77 years, and an average VA of 20/40 (with 20% having VA of 20/100 or worse), 90% of patients were able to successfully complete the self-scan in at least 1 eye, demonstrating the usability of the technology.

Treatment burden can also be decreased by reducing the frequency of injections. One way to accomplish this is to develop drugs with longer durations of action. The initial label dose frequency was monthly for ranibizumab, up to every 2 months for aflibercept, and up to every 3 months for brolucizumab, each after appropriate loading.13,29,30 At present, although the current labels for all 3 drugs include options for dosing every 3 months, the labels for ranibizumab and aflibercept—but not for brolucizumab—state that this dosing interval may be less effective than more frequent dosing.13,29,30

Another option for reducing injection frequency is to recognize that response to anti-VEGF therapy is heterogeneous among patients, and that some patients can be dosed less frequently than indicated by the drug labels. The as-needed dosing strategy—in which eyes are retreated only upon worsening of VA and/or OCT findings—has been shown to be comparable to monthly dosing with frequent monitoring.8,16,31 Effective as-needed dosing is practically difficult because it necessitates regular—likely monthly—disease activity assessments to identify the need for retreatment and duplicate the results of the noninferiority HARBOR trial.

More recently, clinical practice has adopted the treat-and-extend (TAE) approach to anti-VEGF therapy. In this strategy, following the appropriate loading dose, intervals between disease assessment visits are progressively lengthened in 2- to 4-week increments to identify the maximum duration of effect of a given drug in a given patient. Upon recurrence of disease activity, the reassessment interval is typically reduced by 2 to 4 weeks.

Several studies have demonstrated the clinical value of the TAE approach to anti-VEGF dosing [summarized in Table 1].25-37 The TREX-AMD (Treat-and-Extend Protocol in Patients With Wet Age-Related Macular Degeneration) study compared monthly ranibizumab with TAE ranibizumab over 24 months in eyes with nAMD.32 Eyes in the TAE group received at least 3 monthly loading

Table 1. Efficacy Summary of Key Studies Evaluating Treat-and-Extend Dosing Strategies for Neovascular Age-Related Macular Degeneration

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Comparator</th>
<th>Duration, months</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREX-AMD32</td>
<td>Ranibizumab TAE</td>
<td>Ranibizumab monthly</td>
<td>24</td>
<td>• BCVA similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fewer injections with TAE</td>
</tr>
<tr>
<td>TREND33</td>
<td>Ranibizumab TAE</td>
<td>Ranibizumab monthly</td>
<td>12</td>
<td>• BCVA similar [noninferior]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• OCT images similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fewer injections with TAE</td>
</tr>
<tr>
<td>CANTREAT34</td>
<td>Ranibizumab TAE</td>
<td>Ranibizumab monthly</td>
<td>12</td>
<td>• BCVA similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fewer injections with TAE</td>
</tr>
<tr>
<td>LUCAS35</td>
<td>Ranibizumab TAE</td>
<td>Bevacizumab TAE</td>
<td>24</td>
<td>• BCVA similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• OCT images similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fewer injections with ranibizumab</td>
</tr>
<tr>
<td>ATLAS36</td>
<td>Afibercept TAE</td>
<td>None</td>
<td>24</td>
<td>• BCVA improved from baseline in year 1 but less so in year 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• OCT images similar in years 1 and 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fewer injections in year 2</td>
</tr>
<tr>
<td>ALTAIR37</td>
<td>Afibercept TAE 2-week extension</td>
<td>Afibercept TAE 4-week extension</td>
<td>24</td>
<td>• BCVA similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• OCT images similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Injection rates similar</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; OCT, optical coherence tomography; TAE, treat and extend.
doses until resolution of disease activity by both examination and OCT criteria, after which the interdose interval was extended in 2-week increments to a maximum of 12 weeks. Among the 40 TAE eyes and 20 monthly eyes, mean BCVA gains at 24 months were similar (8.7 vs 10.5 letters, respectively; \(P = \sim .5\)), whereas the mean number of injections was significantly lower for the TAE eyes (18.6 vs 25.5, respectively; \(P < .001\)). The mean maximum extension interval was 8.5 weeks, and 17% of patients were successfully extended to 11 to 12 weeks between retreatments. Ocular adverse events (eg, worsening cataract, epiretinal membrane, and progressive macular atrophy) were seen in 5% to 13% of TAE eyes, but in no monthly eyes.

The **TREND** (Treat and Extend) study also compared monthly ranibizumab (n = 327) with TAE ranibizumab (n = 323) for nAMD, but was a much larger study, with 650 treatment-naive eyes.3²³ Eyes in the TAE group began extending after the second monthly injection at month 1, in 2-week increments, to a maximum of 12 weeks, with 2-week reductions upon recurrence of disease activity. At 12 months, BCVA gains were 7.9 letters in the monthly group and 6.6 letters in the TAE group; this difference met the study’s prespecified margin for noninferiority. Likewise, there was no significant difference in OCT central subfield thickness at 12 months between the monthly and TAE groups (-173 vs -169 µm, respectively; \(P = .48\)) and fewer postbaseline visits (8.9 vs 11.2, respectively) than the monthly group. Common adverse events included elevated intraocular pressure and subconjunctival hemorrhage and were of equal frequency between groups.

**CANTREAT** (Canadian Treat-and-Extend Analysis Trial With Ranibizumab) was a comparison of monthly ranibizumab (n = 258) with TAE ranibizumab (n = 268) conducted in Canada.3⁴ This study included S26 eyes, and, as in other studies, treatment was extended in the TAE group after cessation or stability of nAMD disease activity, with shortening of intervisit intervals upon recurrence. At 12 months, noninferiority of TAE to monthly therapy was demonstrated, with mean BCVA gains of 8.4 and 6.0 letters in the TAE and monthly groups, respectively. This was accomplished with fewer injections in the TAE group (9.4 vs 11.8; \(P < .001\)). The nature of adverse events was not described, but the frequency was similar between groups.

**LUCAS** compared ranibizumab and bevacizumab when both were given using the TAE strategy.3⁵ Monthly loading doses were given to achieve disease inactivity, after which the dosing interval was extended in 2-week increments to a maximum of 12 weeks. After 2 years of therapy, visual gains (6.6 vs 7.4 letters, respectively; \(P = .63\)) and decrease in central retinal thickness (122 vs 113 µm, respectively; \(P = .48\)) were similar in the patients receiving ranibizumab (n = 172) or bevacizumab (n = 167), whereas the number of injections was lower in the ranibizumab group (16.0 vs 18.2, respectively; \(P < .001\)). At 2 years, 28% of ranibizumab eyes vs 45% of bevacizumab eyes had residual fluid on OCT. In this study, 2-week reductions in between-visit intervals were effective upon recurrence of disease activity, except for those eyes already maximally extended to 12 weeks, suggesting that more drastic reductions may be warranted in eyes with recurrence at 12-week extension. Although the numbers of each event were small (eg, 3 pseudophakic maculopathy, 3 macular hemorrhage, and 2 BCVA loss > 30 letters), all 11 serious adverse events reported in this study occurred in the bevacizumab group.

**ATLAS** (Afiblercept Treat and Extend for Less Frequent Administration Study) was a nonrandomized, uncontrolled, prospective interventional case series in which 40 eyes with nAMD were treated with afiblercept using the TAE dosing strategy for 2 years.3⁶ All eyes received monthly injections until prespecified criteria for disease inactivity were met, after which treatments were extended in 2-week intervals up to a maximum of 16 weeks, with 2-week reductions upon disease recurrence. The mean number of injections in years 1 and 2 was 8.0 and 6.5, respectively, which produced BCVA improvements of 7.2 letters (\(P < .001\) for change from baseline) and 2.4 letters (\(P = .27\)), respectively. The reduced VA gains in year 2 were not related to loss of exudative control because mean change in central foveal thickness at 1 and 2 years was -209 and -211 µm, respectively. Instead, the investigators postulated that a small number of outlier patients with significant VA reductions during year 2 of the study may have reduced the overall mean BCVA change in a manner that was not representative of outcomes in most patients in the study. Ocular adverse events were limited to a single case of culture-positive endophthalmitis.

The **ALTAIR** study was a comparison of 2 TAE strategies of afiblercept; patients were randomly assigned to either a 2-week (n = 124) or 4-week (n = 123) extension after 3 monthly loading doses.3⁷ Both TAE strategies produced similar BCVA gains at 1 year (mean of 9.0 letters vs 8.4 letters, respectively) and 2 years (mean of 7.6 letters vs 6.1 letters, respectively). Likewise, changes in central retinal thickness were similar at 1 year (-134 µm vs -126 µm, respectively) and 2 years (-131 µm vs -125 µm, respectively). Both groups required a mean of 10.4 injections at 2 years, and approximately 60% were successfully extended to 12 weeks and 40% to 16 weeks. The nature and rates of ocular events (eg, cataract, conjunctival hemorrhage, and dry eye) were similar in both groups as well.

**EMERGING THERAPIES FOR nAMD**

The current array of anti-VEGF drugs—ranibizumab, bevacizumab, afiblercept, and, most recently, brolucizumab—has collectively driven a paradigm shift in the management of nAMD and other retinal vascular diseases. These drugs provide stability of VA in most treated patients and the potential for improved VA in a subset of these patients. Some patients, however, manifest incomplete responses to these agents or require ongoing monthly retreatment. There remains an unmet need for a broader armamentarium of therapies to prevent vision loss in eyes with nAMD while also reducing the treatment burden imposed by current therapies. Numerous novel molecules and drug delivery systems in various stages of clinical development seek to fulfill this unmet need.

**Abicipar Pegol**

Abicipar pegol (abicipar) is a DARPin (designed ankyrin repeat protein). These designer molecules contain an ankyrin repeat domain that can be engineered to bind to any desired target protein with high specificity and binding affinity,3⁸ and, in many cases, are heat stable to temperatures in excess of 80°C.3⁹ In the case of abicipar, its molecular target is all isoforms of VEGF–A (Figure 4A).4⁰,4¹ Like all DARpins, abicipar is a small molecule (34 kDa), which allows for higher dosing on a molar basis (compared with full-sized anti-VEGF antibodies) and may enhance tissue penetration.⁴² After a single intravitreal injection of abicipar 0.4 mg in an early phase 1/2 study in human eyes with diabetic macular edema, the ocular half-life of abicipar was > 13 days, and the median aqueous humor concentration at 3 months remained several orders of magnitude above the half–maximal inhibitory concentration—the concentration needed for ongoing therapeutic anti-VEGF activity (Figure 4B).4² Abicipar is in late-stage clinical development for nAMD and is currently under review by both the FDA and the European Medicines Agency.⁴³ Two double-masked, randomized, phase 3 clinical trials—CEDAR and SEQUOIA—were recently completed.⁴⁴ Both studies compared abicipar 2 mg dosed at fixed intervals of either every 8 weeks or every 12 weeks with ranibizumab 0.5 mg.
dosed monthly. The primary outcome was the proportion of patients with stable BCVA (losing < 15 letters from baseline) at month 12. In a pooled analysis of data from these 2 trials encompassing 1638 subjects that finished the full 104 weeks of the study, this outcome was achieved by 96% of eyes receiving abicipar every 8 weeks, by 94% of eyes receiving abicipar every 12 weeks, and by 97% of eyes receiving ranibizumab at month 12. In a pooled analysis of data from these 2 trials encompassing 1638 subjects that finished the full 104 weeks of the study, this outcome was achieved by 96% of eyes receiving abicipar every 8 weeks, by 94% of eyes receiving abicipar every 12 weeks, and by 97% of eyes receiving ranibizumab at month 12. These comparable outcomes were achieved with vastly different treatment burdens: a total of 10 quarterly injections of conbercept—confirm these findings.49 Conbercept is currently being evaluated in a pair of 2-year global phase 3 trials—PANDA 1 and PANDA 2—in eyes with treatment-naïve nAMD.50,51 The trials compare conbercept 0.5 mg every 8 weeks and 1.0 mg every 12 weeks with aflibercept 2.0 mg every 8 weeks.

### Conbercept

Conbercept is a fusion protein similar to aflibercept, but with an additional VEGF–binding domain. Aflibercept incorporates domain 2 of VEGF receptor 1 and domain 3 of VEGF receptor 2, whereas conbercept adds domain 4 of receptor 2, which decreases the positive charge of the molecule and may reduce adhesion to extracellular matrix.46 Conbercept serves as a soluble VEGF receptor decoy, binding to all forms of VEGF as well as placental growth factor, preventing these molecules from reaching their active receptors and thus blocking their activity. It has a similar binding affinity and vitreous half-life to aflibercept.

The phase 3 PHOENIX study was a 12-month, double-masked, sham-controlled trial conducted in 124 subjects in China.48 The active arm (n = 81) received 3 monthly injections of conbercept 0.5 mg, followed by quarterly injections thereafter, whereas the sham group (n = 43) received 3 sham injections, followed by quarterly active conbercept injections. The primary end point was mean change in BCVA from baseline to month 3, and was +9.20 letters in the conbercept group and +2.02 letters in the sham group (P < .001). At month 12, after the sham group crossed over to active therapy at month 3, mean BCVA changes were +9.98 and +8.81 letters, respectively (P = .64), demonstrating no significant detriment to the 3-month delay in therapy in the sham group. Most of the reported adverse events were related to the injection process (eg, conjunctival hemorrhage), and increased intraocular pressure occurred in 4.9% of conbercept-treated eyes by month 12. Other clinical trials conducted exclusively in China—where the drug is approved for nAMD treatment—confirm these findings.49 Conbercept is a bispecific antibody, in which binding sites for both VEGF-A and angiopoietin-2 (Ang-2) have been incorporated (Figure 5).52 Vascular endothelial cells have a tyrosine kinase transmembrane receptor (Tie-2) that can bind the growth factors angiopoietin-1 (Ang-1) and Ang-2.53 Ang-1 binding to the Tie-2 receptor promotes vascular stability and maintains healthy endothelial barrier function to prevent vascular leakage. Ang-2 is elevated in pathophysiologic states and competes with Ang-1 for binding at the Tie-2 receptor. Ang-2 interrupts the vascular

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Abbreviation: BCVA, best-corrected visual acuity.

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**Table 2.** Best-Corrected Visual Acuity Changes From Baseline and Proportion of Patients* Maintaining Vision at 52 Weeks in the CEDAR and SEQUOIA Phase 3 Trials of Abicipar44,45

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Faricimab has completed phase 2 clinical development for nAMD in a pair of studies: AVENUE and STAIRWAY.55,56 STAIRWAY enrolled 76 patients with treatment-naïve nAMD and randomly assigned them to receive either faricimab 6.0 mg every 12 or 16 weeks or ranibizumab 0.5 mg every 4 weeks for 12 months.57 All faricimab patients received 4 monthly loading doses, with sham injections given as needed to preserve double masking. At week 24, 12 weeks after the last loading dose, 65% of eyes receiving either dose of faricimab exhibited no disease activity, as assessed using prespecified criteria.57 The mean changes from baseline in BCVA at month 12 were +10.08, +11.42, and +9.59 letters with faricimab every 12 weeks, faricimab every 16 weeks, and ranibizumab, respectively, and the mean changes in OCT central subfield thickness from baseline to month 12 were -138.5, -122.5, and -129.9 µm, respectively. No serious ocular adverse events occurred in any eyes, and nonserious ocular adverse events occurred with similar frequency in all 3 groups.57 Phase 3 trials, TENAYA and LUCERNE, are currently proceeding and are fully enrolled.58,59

Port Delivery System

The port delivery system (PDS) is a refillable implant inserted through the pars plana into the vitreous cavity that delivers a therapeutic drug level for an extended period of time.60 In the phase 2 LADDER trial (N = 220), PDS filled with ranibizumab 100 mg/mL provided nAMD disease control for a median of 15 months before the first refill and produced mean BCVA gains from baseline to month 9 of +5.0 letters, which was comparable to that seen with monthly ranibizumab 0.5 mg (+3.9 letters); note that these patients were previously treated with anti-VEGF therapy to confirm responsiveness before entering this trial, accounting for the smaller VA gains than would be expected in treatment-naïve eyes.60 Changes in OCT central foveal thickness to month 9 were also similar in the PDS 100 mg/mL and monthly ranibizumab injection groups. Vitreous hemorrhage occurred in approximately 50% of eyes before optimization of the surgical procedure midway through the phase 2 program, reducing this rate to approximately 4.5%. The phase 3 ARCHWAY trial is currently under way; data are expected this year.61

Other Therapies

Other promising therapies, including both drugs and sustained drug delivery systems, are in earlier stages of development. KSI-301 is an antibody biopolymer conjugate, a 950-kDa protein with an ocular concentration at 3 months after dosing approximately 1000-fold higher than that of aflibercept, which is designed to block all isoforms of VEGF-A.62 GB-102, a depot formulation of sunitinib, a multiple receptor tyrosine kinase inhibitor, acts as a potent pan-VEGF (VEGF-A, -B, -C, and -D) inhibitor. Sunitinib is currently approved in an oral form as a chemotherapy agent for solid tumors.63 Delivered to the vitreous cavity via a 27G needle, the depot slowly releases therapeutic drug levels for up to 6 months between doses, effectively blocking all 3 VEGF receptors (VEGFR-1, -2, and -3).64

Gene Therapy

Several innovative gene therapies for eyes with nAMD are also in development. RGX-314 is a delivery system that uses an adeno-associated virus 8 to deliver a gene encoding an anti-VEGF antibody fragment similar to ranibizumab.64 Following either subretinal or suprachoroidal injection, the anti-VEGF antibody fragment can be detected 2 and 7 weeks post injection in both retina and retinal pigment epithelium/choroid in rat eyes, with a dose-response relationship demonstrating higher tissue levels after 2 injections vs 1 injection. Another gene therapy approach is using an in-office, intravitreal ADVM-022, an AAV7m8 vector designed to deliver gene encoding for aflibercept.65 This therapy has been shown to produce a vitreous aflibercept concentration consistent with therapeutic levels in humans and to prevent CNV in nonhuman primates pretreated 13 months before the experimental induction of CNV.

PANEL DISCUSSION: LOOKING TO THE FUTURE OF THERAPIES FOR nAMD

Dr Singer: In your opinion, does using a novel molecule to target VEGF in the eye translate to better efficacy and treatment longevity?

Dr Khanani: When evaluating a molecule, 3 key attributes come to mind: molar dosing, binding affinity, and pharmacokinetics in the eye. We do not know which of these factors matters the most, but I think that a combination of all 3 should lead to better efficacy and treatment longevity in the clinic.

Dr Eichenbaum: I think that the “proof is in the pudding”, so to speak. These novel designs are innovative and interesting, but the clinical data are most informative, in my opinion.

Dr Holekamp: I agree with Dr Eichenbaum. It will be interesting to see what happens with some of the more novel designs that are not just slightly modified anti-VEGF monoclonal antibodies. The number of patients who can be maintained at a dosing interval longer than every 8 weeks is an important piece of data to consider because it may allow patients to follow up less frequently when using a new agent, thus decreasing the overall burden. Clinical trials have shown differences among new and emerging agents in this regard.

Dr Khanani: As far as data are concerned, resolution of fluid is the most important to me because that is what I treat in the clinic. That being said, in my opinion, agents that dry the fluid better will also be more durable.

Dr Holekamp: Improved fluid resolution does not always correlate with improved VA, which is arguably more relevant to the patient.
Dr Singer: That is true. We are still trying to figure out as a community the relevance of different types of retinal fluid.

Dr Khanani: Safety is also important. As we learn more about the inflammation associated with new and emerging therapies, we might be able to identify patients who are more likely to experience inflammation. In the end, we have to balance safety and efficacy of any treatment option we provide to our patients.

**CASE 1: FLUID RECURRENCE AFTER EXTENSION**

*From the Files of Michael Singer, MD*

A 71-year-old male presented with acute loss of VA. His past medical history included type 2 diabetes and systemic hypertension, and no prior ocular history. On examination, his VA was 20/20 OD and 20/150 OS. He had drusen in both maculae, and retinal pigment epithelium changes and fluid OS (*Figure 6A*). The OCT image confirmed subretinal fluid OS (*Figure 6B*).

Three monthly injections of aflibercept were given, resulting in macular drying (*Figure 7A*) and VA improvement to 20/40. He was extended to 8 weeks and seen at 20 weeks, at which time the fluid recurred and VA worsened slightly to 20/50 (*Figure 7B*).

**Discussion**

*Dr Singh:* This patient failed an extension to 2 months after 3 monthly aflibercept injections. What would you do now?

*Dr Holekamp:* Although I can tolerate a little bit of subretinal fluid, vision here matters. Because vision declined at the same time that subretinal fluid worsened, I think it is time to shorten the treatment interval for this patient and try to get the macula dry. I would do this regardless of anti-VEGF agent being used.

*Dr Eichenbaum:* Would you consider tolerating that fluid and leaving his macula like this? His VA is still surprisingly good with that amount of subretinal fluid. One might opt to tolerate the fluid, given the relative Snellen VA stability, but I would prefer the macula be drier than that because the patient was anatomically dryer with better VA at the preceding visit.

*Dr Singer:* I agree. Given that he would need ongoing monthly injections with aflibercept, I opted to switch to brolucizumab in hopes of achieving and maintaining a dry macula and improved VA with fewer injections. We have accomplished this with brolucizumab extended to every 10 weeks now.

**Case 1 Summary**

*Dr Singer:* Our treatment goal is to eliminate as much fluid as possible. Residual intraretinal fluid is associated with loss of vision. I believe that the subretinal fluid shadow seen on OCT images may consist of different factors early in the disease process as compared with later in disease process. Although the goal is still to get the retina as dry as possible, I am willing to settle for residual subretinal fluid in the longer term so long as vision does not worsen.

**CASE 2: PERSISTENT FLUID**

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

A 70-year-old female has been under care for nAMD for 7 years. She had received a total of 15 bevacizumab injections, 8 ranibizumab injections, and 37 aflibercept injections, 8 of which were given in 2019. In this patient, VA fluctuates between 20/25 and 20/40. Despite multiple attempts to extend the interval between injections, she required injections consistently every 4 to 5 weeks. *Figure 8* shows an OCT image of her eye 6 weeks after an aflibercept injection, revealing persistent fluid when treatment was extended beyond 5 weeks.

**Discussion**

*Dr Khanani:* Given the tremendous treatment burden—visits and injections every 5 weeks, even with a longer-acting anti-VEGF drug such as aflibercept—what would you do now?

*Dr Holekamp:* It is favorable that this is subretinal fluid because even recurrent subretinal fluid can be compatible with good vision long term in patients. We know this from the FLUID study.67 This is, however, a significant amount of subretinal fluid. I would make a change and switch agents.

*Dr Eichenbaum:* Because you have already tried every other anti-VEGF agent for a minimum of 8 injections, I would discuss a switch to brolucizumab with the patient in hopes of extending beyond 5 weeks.

*Dr Khanani:* The patient and I agreed that brolucizumab was the best next step. Four weeks after the last aflibercept injection, BCVA was 20/30 and the OCT image revealed trace subretinal fluid and a small pigment epithelial detachment (*Figure 9A*). Brolucizumab was injected at that time, and at 6 weeks postinjection, BCVA was 20/25 and the macula was completely dry (*Figure 9B*). We reassessed every 2 weeks to determine the optimal extension interval, and the VA and OCT remained stable until week 14 (*Figure 9C*), when the appearance of subtle subretinal fluid (and BCVA 20/30) led us to re-treat. With brolucizumab, she can now be injected every 3 months instead of every 5 weeks with aflibercept.

*Dr Singer:* Not only is her disease better, but her treatment burden is significantly reduced. Longer-acting anti-VEGF therapies such as this one are very likely to improve overall adherence to follow-up and therapy, especially among our more rural patients, who live far from our treatment centers.
Case 2 Summary

Dr Khanani: This case highlights the treatment burden and frequent visits required by some patients with nAMD. As with this patient, there are patients who require monthly anti-VEGF injections, or else their disease is not controlled. Emerging molecules may be beneficial in addressing this unmet need, as shown by an excellent response to recently approved brolucizumab.13

CASE 3: SWITCHING ANTI-VEGF AGENTS

From the Files of David Eichenbaum, MD

An otherwise healthy 67-year-old male presented with distortion and blurry vision OS. His BCVA was 20/25 OD and 20/63 OS. Figure 10A shows his baseline OCT images and reveals subretinal fluid. Three monthly loading doses of aflibercept were given, after which TAE was initiated. Extension was attempted 3 times over 2 years, but the patient never achieved an interval beyond 5 weeks because of recurrent subretinal fluid with stable BCVA of 20/50 after 6 weeks (Figure 10B). The patient was unhappy with the frequency of visits and injections and was switched to brolucizumab. Five weeks later, BCVA was 20/32 and there was no fluid (Figure 10C), so the patient was re-treated and extended to 6 to 7 weeks. At that visit—the most recent encounter—BCVA and the OCT images remained stable (Figure 10D), so the patient was re-treated and extended to 7 to 8 weeks.

Discussion

Dr Eichenbaum: What are your indications for switching to a different anti-VEGF agent?

Dr Singer: When initiating therapy in treatment-naïve patients, I give a minimum of 4 injections, and if macular dryness is not achieved, I consider switching to a different agent. Also, as this case illustrates, even if we do achieve macular dryness, I would consider switching from a shorter-acting agent to a longer-acting agent to decrease the treatment burden.

Dr Holekamp: We know from all the randomized clinical trials that even with frequent, consistent anti-VEGF treatments, some eyes never achieve dryness. Thus, it is exciting to see the development of new agents that may allow us to reach 2 goals: better drying and decreased burden. These are the 2 reasons I would consider switching to a new agent.

Dr Khanani: I usually consider switching after 3 to 6 monthly injections if I see persistent disease activity. This patient has clearly benefited from switching to brolucizumab. In the future, we will likely have other options to switch to—such as abicipar, faricimab, and PDS—and patients such as the one in Case 3 may benefit from these options. Each agent or delivery system may have a different efficacy and safety profile, and we always have to balance safety and efficacy whenever we use a new agent.

Dr Eichenbaum: How rapidly do you think physicians and patients will embrace some of the emerging therapies that may offer even longer durations of action than those of our current drugs?

Dr Singer: In my experience, patients will do whatever it takes to preserve their VA. It is exciting to have so many current and emerging therapies with such a variety of attributes. We are approaching the era of individualized therapy for nAMD, in which we will have the luxury of many treatments from which to choose and can select the agent that best fits the needs of a particular patient.

Case 3 Summary

Dr Eichenbaum: Switching agents in patients who are intolerant or nonresponsive to frequent injections is a reasonable strategy to try to mitigate the burden of nAMD care. As we see more, potentially longer-lasting agents come into the treatment space, we can hope to have more options with a lower treatment burden for patients.

TAKE-HOME POINTS

• The treatment burden in nAMD limits optimal anti-VEGF dosing rates in real-world clinical practice, resulting in suboptimal VA outcomes compared with those reported in clinical trials

• Multiple studies now demonstrate that the TAE dosing regimen for anti-VEGF therapy provides similar VA outcomes as regular injections every month or 3 months, with a significantly lower injection rate over time

• Novel drugs, devices, and platforms with longer durations of action attributable to greater tissue penetration and/or higher binding affinities vs current therapies provide options for optimizing VA outcomes with a lesser treatment burden

• New drugs and novel delivery systems provide functional (VA), structural (OCT), and safety outcomes comparable to those achieved with anti-VEGF injections administered every 4 to 12 weeks
1. Which drug was shown to maintain BCVA better than both sham injection and PDT with verteporfin in phase 3 trials?
   a. Bevacizumab
   b. Ranibizumab
   c. Aflibercept
   d. Brolucizumab

2. Aflibercept dosed every demonstrated noninferior maintenance of BCVA compared with monthly ranibizumab therapy.
   a. Month
   b. 2 months
   c. 3 months
   d. Both a and b

3. In the phase 3 HAWK and HARRIER trials, of eyes were maintained on brolucizumab 6 mg every 12 weeks at month 12.
   a. 12% to 16%
   b. 34% to 37%
   c. 51% to 56%
   d. 75% to 78%

4. In the CEDAR and SEQUOIA phase 3 trials comparing abicipar dosed every 2 or 3 months with monthly ranibizumab, the 24-month BCVA and OCT outcomes were comparable in all 3 groups. This was achieved with quarterly injections of abicipar and monthly injections of ranibizumab.
   a. 5, 14
   b. 25, 10
   c. 10, 25
   d. 16, 24

5. Which of the following characteristics likely contributes to abicipar’s extended duration of action (up to 12 weeks)?
   a. High target specificity from its ankyrin repeat domain
   b. Higher molar dosing due to its small size
   c. Long half-life in ocular tissues
   d. All the above

6. Faricimab was shown in the phase 2 STAIRWAY trial to suppress nAMD disease activity for up to 16 weeks following each dose. One possible explanation for this extended duration of activity is:
   a. Faricimab is a small DARPin with a relatively long ocular half-life
   b. Faricimab inhibits the activity of VEGF-A, VEGF-B, and VEGF-C
   c. Faricimab inhibits both the VEGF and Tie-2 pathways
   d. Faricimab inhibits platelet-derived growth factor

7. The PDS is a sustained-release platform with a median time to refill of up to every _______ months when delivering ranibizumab 100 mg/mL.
   a. 3
   b. 6
   c. 10
   d. 15

8. Which of the following anti-VEGF dosing strategies typically has the least favorable VA outcomes?
   a. Regular injections every 1 to 3 months as indicated for specific drugs
   b. TAE to increase the interval between injections while still suppressing disease activity
   c. As needed when VA or OCT image appearance worsens
   d. Every 10 weeks regardless of OCT image appearance

9. A patient with newly diagnosed nAMD has no disease activity after 3 monthly loading doses of anti-VEGF therapy. According to the TAE dosing strategy, the next dose should be given ___ weeks later.
   a. 2
   b. 4
   c. 6
   d. 9

10. A patient's nAMD was stable with extension of anti-VEGF injections to every 10 weeks, but then recurrent subretinal fluid was seen at a scheduled 10-week follow-up. What is the best next step?
    a. Give 3 additional monthly loading doses and then begin extending the treatment interval
    b. Re-treat and reevaluate in 4 weeks
    c. Reevaluate in 2 weeks without re-treating
    d. Re-treat and reevaluate in 8 weeks