

# Review of Neovascular Age-Related Macular Degeneration Treatment Options

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## Disease Overview

Age-related macular degeneration (AMD) causes irreversible destruction of the macula, which leads to loss of the sharp, fine-detail, “straight ahead” vision that is required for activities such as reading, driving, recognizing faces, and seeing in color. It is a leading cause of irreversible visual impairment in the world.<sup>1,2</sup> Over the past 15 years, anti-vascular endothelial growth factor (VEGF) agents have profoundly transformed the management of neovascular AMD (nAMD) and are credited with unprecedented improvements in vision preservation and quality of life for millions of patients in the United States. After 2 years of treatment with an anti-VEGF agent, more than 95% of patients can expect to remain within 3 lines of their baseline visual acuity, and up to 40% can expect an improvement of 3 lines in the affected eye over baseline.<sup>3</sup> Evidence suggests that real-world outcomes lag behind those documented in clinical trials.<sup>4</sup> Analysis of medical claims data in the United States has found that patients with newly diagnosed nAMD receive fewer anti-VEGF injections and less frequent monitoring.<sup>5</sup> Additionally, a recent cohort study in the United States found that more than 20% of patients receiving an anti-VEGF agent discontinued treatment and did not follow up.<sup>6</sup> The relentless chronicity of nAMD most likely contributes to less than optimal outcomes. Some patients require regular anti-VEGF agent injections despite already receiving treatment for at least 10 years.<sup>7</sup>

Even with the profound benefits that available anti-VEGF agents have provided, innovations are needed in nAMD management. Investigational agents that could improve outcomes include a continuous delivery system for ranibizumab, an FDA-approved source of intravitreal bevacizumab, new anti-VEGF agents that extend the dosing interval, gene therapy to deliver anti-VEGF proteins,<sup>8</sup> and agents with new mechanisms of action. This article provides an overview of AMD epidemiology, pathophysiology, diagnosis, and prevention, while also reviewing current and emerging anti-VEGF agents and management approaches.

## Staging and Pathophysiology of AMD

AMD stages are characterized as early, intermediate, and late. In general, early AMD, also referred to as age-related maculopathy,

## ABSTRACT

Due to an aging population, visual impairment from neovascular age-related macular degeneration (nAMD) is increasing in the United States. Despite unprecedented improvements in vision preservation that patients can achieve with anti-vascular endothelial growth factor (VEGF) agents, innovations are needed to reduce the burden of intravitreal injections and improve outcomes in patients who do not respond adequately to currently available agents. The best present option for vision preservation is a “zero-tolerance for fluid” schedule of monitoring and intravitreal injections that patients may need to follow for many years. This treatment burden has resulted in patients not achieving optimal benefit or even falling through the cracks. This article reviews state-of-the-art management approaches including as-needed and treat-and-extend dosing regimens designed to reduce treatment burden.

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For author information and disclosures, see end of text.

has multiple small lipid deposits called drusen (<63 μm) and a smaller number of medium drusen (63-125 μm) under the retina, or mild pigmentation abnormalities of the retinal pigment epithelium (RPE) in at least 1 eye.<sup>9</sup> Intermediate AMD is characterized by at least 1 large druse (>125 μm), retinal pigment abnormalities, or geographic atrophy of the RPE that does not involve the center of the fovea. Late AMD is vision-threatening. As shown in **Table 1**,<sup>9</sup> it is categorized as either pure geographic atrophy involving the foveal center (eg, dry) or neovascular (eg, wet).<sup>9</sup> In geographic atrophy, degeneration of the RPE in the foveal center leads to photoreceptor apoptosis and a loss of central vision; there is no current treatment. In nAMD (eg, wet AMD), choroidal neovascularization (CNV) leads to uncontrolled growth of new leaky blood vessels under the macula.<sup>9</sup>

VEGF-A, -B, -C, -D, virally encoded VEGF-E, and placental growth factor are members of a family of proteins that regulate vascular permeability in the retina.<sup>10</sup> VEGF-A, the principal driver of neovascularization in AMD, induces angiogenesis and increases vascular permeability and inflammation. Over time, this causes progressive degeneration of photoreceptors and the RPE, and retinal fluid can accumulate, leading to edema and functional deterioration.

### Epidemiology of AMD

The risk of late AMD, including nAMD and geographic atrophy, increases exponentially in advanced age.<sup>12,11</sup> The Beaver Dam Eye Study examined the incidence of disease in a cohort of patients aged 43 to 86 years.<sup>11</sup> The 15-year cumulative incidence in the entire cohort was 14.3% for early AMD and 3.1% for late AMD. For those aged 75 years or older, the cumulative incidence was 24% for early and 8% for late AMD.<sup>11</sup> A meta-analysis of studies that used fundus photography and standardized protocols to assess disease prevalence found a progressive increase in the incidence of both early and late AMD with age.<sup>2</sup> Prevalence increased rapidly after age 75 years, especially in those of European descent. The overall prevalence of late AMD across all ethnicities was 0.15% for those aged 50 to 59 years, 0.47% for those aged 60 to 69 years, 1.46% for those aged 70 to 79 years, and 3.21% for those aged 80 to 84 years.<sup>2</sup>

AMD is more prevalent in individuals of European descent compared with Asian descent.<sup>2</sup> Late AMD affects white individuals more than other racial groups.<sup>1</sup> The racial make-up of patients with late AMD was 89% white, 4% African American, and 4% Hispanic American. Women, who usually have longer life expectancy than men, accounted for 65% of late AMD cases in 2010.<sup>1</sup>

Due to an aging population and increasing life expectancy, the number of Americans with late AMD, including nAMD and geographic atrophy, is increasing.<sup>1</sup> The number of cases rose from 1.75 million in 2000 to 2.07 million

in 2010, an increase of 18%, and is expected to increase to almost 3.7 million in 2030 and 5.4 million in 2050. Although white individuals will continue to account for the majority of patients, cases of AMD in Hispanic Americans are expected to increase almost 6-fold by 2050.<sup>1</sup> Whereas the incidence of late AMD is increasing, a study that examined the 5-year risk of disease across generations in the 20th century suggests that the incidence of early or intermediate AMD has declined by 60% with each successive generation.<sup>12</sup> This suggests that modifications in environment, behavior, or lifestyle may reduce the risk of AMD.

### Risk Factors for Progression to Late AMD

Genetic and environmental factors contribute to the development of late AMD.<sup>13</sup> Modifiable risk factors for progression to nAMD, identified in the Age-Related Eye Disease Study (AREDS), include smoking and body mass index.<sup>14</sup> White race and less secondary education were among other risk factors.<sup>14</sup> Occupational sunlight exposure has been identified as a potential risk factor for AMD.<sup>15</sup> However, a recent meta-analysis of almost 44,000 patients found that sunlight exposure was not associated with an increased risk of disease (odds ratio [OR], 1.1; 95% CI, 0.98-1.23).<sup>16</sup> Although aspirin was identified as a possible risk factor for AMD in some observational studies, a meta-analysis based on more than 171,000 patients did not find an association between aspirin use and AMD.<sup>17,18</sup> The American Academy of Ophthalmology (AAO) recommends that patients who have been told by their physician to take aspirin should continue to take it.<sup>9</sup>

The largest genome-wide association study conducted to date identified 52 common and rare AMD gene variants distributed across 34 loci.<sup>19</sup> The authors reported that susceptibility for progression to advanced AMD varies widely among individuals based on their gene variants. For example, individuals who rank in the top 10% of genetic risk have a 44-fold higher relative risk of developing advanced AMD compared with individuals in the lowest 10%. The identification of genetic variants is advancing our understanding about the complex biology of AMD and pinpointing mechanisms of disease that are potential therapeutic targets.<sup>19</sup>

### Diagnosis and Monitoring of Neovascular AMD

A comprehensive dilated eye examination is often necessary to diagnose early or intermediate AMD because it is usually asymptomatic.<sup>9</sup>

**TABLE 1.** Dry versus Wet AMD<sup>9</sup>

Dry (geographic atrophy)	Wet (neovascular AMD)
<ul style="list-style-type: none"> <li>• About 90% of AMD cases</li> <li>• Can become “wet”</li> <li>• Drusen form on the macula</li> <li>• No angiogenesis</li> <li>• No current treatment</li> </ul>	<ul style="list-style-type: none"> <li>• About 10% of AMD cases</li> <li>• Accounts for 90% of central visual acuity loss</li> <li>• Neovascularization of the macula</li> <li>• Angiogenesis driven by VEGF</li> <li>• Treated with intravitreal anti-VEGF agents</li> </ul>

AMD indicates age-related macular degeneration; VEGF, vascular endothelial growth factor.

AMD is generally diagnosed through a dilated fundus examination, during which the retina is examined for drusen, which appear as yellow deposits, and pigmentary changes caused by waste products from damaged retinal cells. Diagnostic tools used by retinal specialists for diagnosis and monitoring treatment response to anti-VEGF agents include optical coherence tomography (OCT), fluorescein angiography, and more recently OCT-angiography.<sup>9</sup> Fluorescein angiography detects leaky blood vessels characteristic of late AMD. Signs and symptoms of nAMD that can appear and progress over days to weeks include loss of both far and near vision, sudden visual distortion (particularly wavy lines), central vision loss, and changes in color vision.<sup>20</sup>

AMD may be underdiagnosed in the United States, as it was found in a recent cross-sectional study that approximately 25% of eyes were found to have AMD despite there being no diagnosis of the disease by primary eye care ophthalmologists or optometrists in the medical record.<sup>21</sup> Thirty percent of patients with undiagnosed AMD had large drusen, indicating intermediate AMD. Early diagnosis of nAMD is crucial because patients can lose an average of 3 to 5 lines of vision during progression from intermediate to nAMD.<sup>22</sup> Further, vision outcomes 1 and 2 years after initiation of an anti-VEGF agent are strongly predicted by visual acuity at the time treatment is started.<sup>23</sup>

Patients with intermediate AMD who are at high risk for progression to nAMD can self-monitor for changes in central vision that herald this development. The traditional method, practiced since the 1950s, is to periodically check an Amsler grid to test if lines on the grid disappear or appear wavy.<sup>24</sup> However, Amsler grid monitoring has low detection rates, likely because of low sensitivity and patient adherence. Monitoring with a macular visual-field testing method, preferential hyperacuity perimeter (PHP), has greater sensitivity and specificity.<sup>24</sup> PHP home monitoring is emerging as a telemedicine solution to more efficiently monitor the growing population of elderly patients at risk for late AMD.<sup>25</sup> In the 2018 annual American Society of Retina Specialists (ASRS) survey, 25% of US retinal specialists reported using PHP home monitoring.<sup>26</sup>

The ForeseeHome program (Notal Vision) is the first validated and FDA-approved PHP home monitoring system to detect visual distortions in nAMD.<sup>27</sup> It is indicated for use by patients with intermediate AMD in both eyes, or those with intermediate AMD in 1 eye and CNV in the other. Patients with best corrected vision of 20/60 can monitor PHP daily with a device at home, a task that takes approximately 3 minutes per eye.<sup>28</sup> The data are transmitted to a central data center via telemonitoring where they are compared with a normative database and the patient's previous history. A significant change in vision triggers notification of the patient's ophthalmologist.<sup>28</sup> Medicaid previously covered the program, but that is currently being challenged.

The development of more advanced at-home monitoring technology is expected to change the treatment paradigm in nAMD. The

FDA recently granted breakthrough device designation to Notal Home OCT (Notal Vision), a home-based OCT device that is being developed to monitor nAMD.<sup>29</sup> This system uses artificial intelligence and a machine-learning algorithm to detect retinal fluid changes on OCT performed by the patient at home. Results are relayed via a cloud-based platform similar to the one used by ForeseeHome. The company expects it to reach the market in 2020.<sup>29</sup> Technology similar to this has the potential to substantially reduce the monitoring burden associated with zero-tolerance for fluid OCT monitoring.

## Prevention of AMD

The use of supplements to prevent progression in selected patients with AMD is based on the single clinical trial AREDS. In this study of more than 4700 patients who were followed for a mean of 6.3 years, a supplement containing vitamins C and E, beta-carotene, and zinc reduced progression of intermediate or advanced AMD in the fellow eye to advanced AMD.<sup>30</sup> Patients with intermediate AMD in 1 or both eyes or advanced AMD in 1 eye had reduced progression to advanced AMD (OR, 0.66; 99% CI, 0.47-0.91) and reduced risk for vision loss (OR, 0.73; 99% CI, 0.54-0.99). Participants with less severe disease had no benefit.<sup>30</sup> Treatment of 13 patients with immediate or advanced AMD with this supplement for 5 years is expected to prevent 1 patient from progressing to severe AMD.<sup>31</sup>

The AREDS2 study altered the original AREDS formula in different study arms.<sup>32</sup> In the AREDS2 study, beta-carotene was replaced with lutein and zeaxanthin because of the association between beta-carotene and lung cancer in smokers. Omega-3 fatty acids (DHA 350 mg, EPA 650 mg) were added to determine if there would be a benefit. These formulation changes did not impact results with the original formulation. In other words, substituting lutein plus zeaxanthin for beta-carotene is reasonable; however, adding omega-3 fatty acids was found not to be beneficial to prevent progression of intermediate AMD to advanced AMD.<sup>32</sup> The AAO recommends that an antioxidant vitamin and mineral supplement consistent with the products used in the AREDS and AREDS2 trials be considered in patients with intermediate or advanced AMD.<sup>9</sup> Patients with an earlier stage of AMD or individuals who do not have the disease should be advised that there is no evidence that supplementation is helpful in these cases.

## Current Treatment Options and Management Approaches

Anti-VEGF agents have had a significant impact on the management of nAMD, which was illustrated by the explosive growth in intravitreal injections given to Medicare part B recipients over the past 15 years. Whereas fewer than 3000 intravitreal injections (this includes diabetic retinopathy) were given in the year 2000, at least 2.6 million injections of ranibizumab and aflibercept were administered in 2014.<sup>33</sup> Clinical practice guidelines from medical

organizations in the United States and Europe concur that anti-VEGF agents are first-line treatment of nAMD because they have been shown to improve visual and anatomic outcomes over other therapies.<sup>9,20,34,35</sup> The use of earlier treatment strategies for nAMD, including laser photocoagulation and photodynamic therapy, have largely been supplanted by anti-VEGF agents.<sup>9,33</sup>

Anti-VEGF treatment options for nAMD have evolved since pegaptanib, the first intravitreal anti-VEGF formulation, received FDA approval in 2004. Pegaptanib is no longer routinely used in clinical practice because it did not substantially improve visual acuity in clinical trials of new-onset nAMD.<sup>9</sup> Since then, the FDA approved ranibizumab in 2006 and aflibercept in 2011.<sup>34</sup> Off-label prescribing of bevacizumab is also a treatment option,<sup>36,37</sup> and it has remained a possibility since then because demonstrated efficacy is noninferior to ranibizumab.<sup>34</sup> The properties of current anti-VEGF agents are compared in [Table 2](#).<sup>33,38-42</sup>

### Anti-VEGF Agent Safety

Ocular severe AEs of intravitreal anti-VEGF therapy include rare reports of infectious and noninfectious endophthalmitis, retinal detachment, and increased intraocular pressure.<sup>9,34</sup> Whereas systemic AEs have periodically been raised as a concern, a large body of evidence indicates that the risk of systemic AEs with intravitreal




injections of anti-VEGF agents remains below the level of detection.<sup>43,44</sup> A 2014 Cochrane review did not find a difference in the risk of serious systemic AEs between intravitreal ranibizumab and bevacizumab.<sup>45</sup> Results of a 2019 Cochrane review that evaluated aflibercept, bevacizumab, and ranibizumab found no difference in serious systemic AEs between anti-VEGF agents or control groups.<sup>46</sup>

### Formulation Issues in Product Selection

Despite a cost benefit for intravitreal bevacizumab, there are important caveats to its use. The sterile compounding that is needed to prepare intravitreal injections provides an opportunity for contamination to occur. Periodically, outbreaks of bacterial and fungal endophthalmitis involving preservative-free bevacizumab have been associated with morbidity and vision loss.<sup>47</sup> In addition, variable concentrations of active drug and silicone oil droplets have been reported with repackaged syringes of bevacizumab from compounding pharmacies.<sup>48,49</sup> Managed care organizations that obtain intravitreal bevacizumab from compounding pharmacies must comply with state legislation and FDA sterile compounding guidelines that were adopted after the New England Compounding Center multistate fungal meningitis outbreak in 2012.

Traditionally, anti-VEGF agents for intravitreal injection have been provided in glass vials. The transfer from vial to syringe before

**TABLE 2.** Properties of Anti-VEGF Agents<sup>33,38-42</sup>

	Aflibercept (Eylea, Regeneron)	Bevacizumab (Avastin, Genentech)	Ranibizumab (Lucentis, Genentech)
Pharmacology	 VEGF-Trap (decoy)	 Monoclonal antibody	 Antibody fragment
Molecular weight	115 kDa	149 kDa	48 kDa
Target	All VEGF-A isoforms VEGF-B PlGF	All VEGF-A isoforms	All VEGF-A isoforms
K <sub>d</sub> for VEGF <sub>165</sub>	0.49 pM	58 pM	46 pM
Estimated intravitreal half-life	4.8 days	5.6 days	3.2 days
FDA-approved indications	nAMD; DME; DR, macular edema after RVO	Not FDA approved for ophthalmic use	nAMD; macular edema after RVO; DME; DR; mCNV
Intravitreal injection dosage regimen for nAMD	2 mg at weeks 0, 4, and 8 then q 8 weeks, although some patients may need q 4 week doses. After first year, may give q 12 weeks for selected patients.	1.25 mg q 4 weeks	0.5 mg q 4 weeks
Formulation	2 mg/0.05 mL single-use vial	25 mg/mL; 4 or 16 mL vials	0.3 mg or 0.5 mg/0.05 mL single-use vial 0.5 mg/0.05 mL single-use syringe

AMD indicates age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy; kDa, kilodalton; mCNV, myopic choroidal neovascularization; nAMD, neovascular age-related macular degeneration; PlGF, placental growth factor; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

the injection is an extra step in the process that poses a risk for bacterial contamination. While packaging in prefilled syringes is more efficient and can potentially reduce the risk of endophthalmitis, ranibizumab is the only agent that is currently available as a prefilled syringe. A recent multicenter retrospective study conducted in the United States and Japan compared the incidence of endophthalmitis with conventional vials and prefilled syringes of ranibizumab.<sup>50</sup> It was found that culture-positive endophthalmitis was significantly reduced with prefilled syringes (OR, 0.19; 95% CI, 0.045-0.82;  $P = .025$ ). This represented an incidence of 0.013% (1 in 7516 injections) with vials and 0.0026% (1 in 39,204 injections) with prefilled syringes. Vision loss after culture-positive endophthalmitis was significantly greater with vials than prefilled syringes (4.45 vs 0.38 lines lost;  $P = .0062$ ).<sup>50</sup>

Periodic clusters of ocular inflammation cases have been reported with aflibercept since it became available in the United States.<sup>51-53</sup> The first cluster of 15 cases occurred within 3 months of marketing, prompting the ASRS to form a subcommittee to monitor and report on these events.<sup>51</sup> The committee recently summarized the most recent clusters of cases reported to the organization.<sup>53</sup> Between May 2017 and February 2018, sterile inflammation was reported in 68 eyes in 66 patients. Although a total of 26 aflibercept lots were involved, 4 lots accounted for 56% of cases.<sup>53</sup> Analysis by the manufacturer found an association between certain batches of syringes that were co-packaged with aflibercept.<sup>54</sup> The annualized rate of intraocular inflammation with the identified syringes was 8 to 12 reports per 10,000 vials. After the lots and syringes were removed from the market, the annualized rate of intraocular inflammation returned to the usual rate of 1 to 4 reports per 10,000 vials.<sup>54</sup>

The syringes used to inject anti-VEGF agents are not designed for intravitreal administration. Some of them have been reported to release silicone droplets that have the potential to cause “floaters” that obstruct the patient’s vision.<sup>49</sup> A recent study suggests the risk of silicone droplets is increased with certain syringe brands and flicking the syringe.<sup>55,56</sup> Among syringes available in the United States, silicone oil was released the most by Terumo 0.5 mL and BD Ultra-Fine 0.3 mL, and the least by BD Tuberculin 1 mL and Exel 0.3 mL.<sup>55</sup> A case-control study in Brazil linked inflammation after aflibercept intravitreal injections with silicone oil droplets from a specific brand of syringe.<sup>56</sup> All of the issues raised here illustrate the complexity of intravitreal administration and the potential for formulation-specific problems to impact product selection.

### Medical Society Recommendations for Anti-VEGF Agents in Neovascular AMD

Clinical practice guidelines from the United States and Europe commonly agree that 2 years of treatment with an available intravitreal anti-VEGF agent is safe and effective.<sup>7,9,20,34,35</sup> Bevacizumab and ranibizumab had comparable efficacy in the Comparison of

AMD Treatment Trial (CATT), the Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) trial, and the Groupe d’Etude Français Avastin versus Lucentis dans la DMLA néovasculaire (GEFAL) study. Aflibercept and ranibizumab had comparable efficacy in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1, VIEW 2) trials.<sup>34</sup> A caveat is that bevacizumab and aflibercept have not been compared head-to-head.<sup>7</sup> In the 2018 ASRS survey, the first-line agent of US retinal specialists for nAMD was bevacizumab (70.2%), followed by aflibercept (16.4%), and ranibizumab (12.8%).<sup>57</sup>

### Dosing and Monitoring of Anti-VEGF Agents

FDA-approved regimens of anti-VEGF agents require an injection every 4 weeks or as needed after 3 loading doses for ranibizumab.<sup>40</sup> For aflibercept, injections are FDA approved to be administered every 4 weeks or every 8 weeks after 3 loading doses.<sup>39</sup> In August 2018, the aflibercept prescribing information was revised to allow the dosing interval to stretch to every 12 weeks in the second year of treatment.<sup>39</sup> This change is based on data from the second year of the VIEW trials in which patients were treated “as needed” based on monitoring every 4 weeks, with a maximum dosing interval of every 12 weeks.<sup>58</sup> Criteria for early retreatment included new or persistent fluid on OCT, an increase in central retinal thickness of greater than or equal to 100  $\mu\text{m}$  over the lowest previous value, loss of 5 or more letters from the best previous score in conjunction with recurrent fluid on OCT, new-onset classic neovascularization, new or persistent leak on fluorescein angiography, or new macular hemorrhage.<sup>58</sup>

Regular OCT monitoring is a crucial aspect of regimens that extend the dosing interval because detection of intraretinal cystoid spaces or subretinal fluid (SRF) during maintenance anti-VEGF therapy signals CNV activity and the need to intensify anti-VEGF therapy.<sup>9,58</sup> In the 2018 ASRS survey, almost half of US retinal specialists considered recurrent intraretinal or subretinal fluid to be the most important indicator of disease activity.<sup>26</sup> OCT also detects central retinal thickness and other signs of disease activity such as pigment epithelial detachment. The coalescence of small soft drusen into a large mass, referred to as a drusenoid pigment epithelial detachment, is a predictor of vision loss.<sup>59</sup> Because any fluid accumulation indicates disease activity that requires more intensive anti-VEGF therapy, close monitoring with zero-tolerance for fluid has become the principle of OCT monitoring.<sup>58</sup>

### As-Needed versus Treat-and-Extend Approach

A treat-and-extend regimen gradually extends the dosing interval in stable patients who demonstrate no disease activity on regular OCT monitoring.<sup>60</sup> In a treat-and-extend algorithm, the treatment interval is gradually increased in 2-week or 4-week increments until a maximum interval of 12 to 16 weeks is reached. If disease

activity is observed, depending on severity, the treatment interval is reduced or reverts to monthly dosing. Treat-and-extend regimens may theoretically reduce the risk of intraocular pressure elevation over time compared with monthly dosing.<sup>60</sup>

As-needed regimens monitor patients closely and give another injection when recurrent disease activity is detected, whereas treat-and-extend regimens maintain treatment at an extended interval with the goal of preventing disease recurrence.<sup>60,61</sup> Although as-needed regimens may reduce the number of injections, patients must still adhere to monthly disease activity monitoring. Because as-needed dosing is not as proactive as treat-and-extend dosing, it may allow for recurrence of disease activity and may culminate in vision loss for some patients.<sup>60,61</sup> Clinicians may prefer an as-needed regimen for patients who have a very high risk of geographic atrophy.<sup>60</sup> Evolving data suggest that greater anti-VEGF exposure may predispose patients to develop vision loss from geographic atrophy, which is now referred to as macular atrophy in treated eyes.<sup>62</sup> Notably, undertreatment with anti-VEGF agents remains a significant problem in managing patients with wet AMD.<sup>5</sup> In a 2015 ASRS survey, almost 65% of US respondents preferred treat-and-extend regimens for managing active nAMD.<sup>7</sup>

### Individualization of Anti-VEGF Therapy

Retinal specialists need access to different anti-VEGF agents to individualize therapy. Although they may be clinically equivalent in large-scale clinical trials, patients may respond differently to specific anti-VEGF agents. Patients with nAMD are a heterogeneous group who differ widely according to needed treatment intensity. Disease activity can be suppressed with an injection interval ranging from 4 to 12 weeks in approximately 10% to 20% of patients.<sup>7</sup> The duration of VEGF suppression varies among patients and anti-VEGF agents.<sup>61</sup> This could relate to differences in size and affinity for VEGF-A.<sup>34,39-41</sup> Therefore, matching an individual patient to the appropriate anti-VEGF agent, dosing approach (ie, fixed, as-needed, or treat-and-extend), and dosing interval is complicated and should not be constrained by limiting clinician access to treatment options.

Anti-VEGF agents have specific attributes that may benefit individual patients based on their priorities and goals for treatment. For example, bevacizumab is an option for patients with end-stage AMD with poor visual acuity and whose highest priority is avoiding out-of-pocket expenses. An analysis based on data from the CATT found it more cost-effective compared with ranibizumab in newly diagnosed patients aged 80 years or older.<sup>63</sup> On the basis of potentially greater safety, ranibizumab may be the preferred agent for patients who are aged 85 years or older. Results from a European Medicines Agency Public Assessment report for aflibercept demonstrated a potentially higher rate of cerebrovascular events with aflibercept compared with ranibizumab in patients aged 85 years or older.<sup>64</sup> In a meta-analysis of ranibizumab AEs in this age group,

there were no reports of an increase in the risk of total nonocular serious AEs, arterial thromboembolic events, cardiovascular events, or Antiplatelet Trialists' Collaboration events compared with controls. There were too few cerebrovascular events or deaths to evaluate these end points.<sup>65</sup>

It is essential for retinal specialists to have ready access to treatment options for patients who do not respond adequately to initial treatment. In the 2018 ASRS survey, almost 80% of US retinal specialists considered switching to another anti-VEGF agent when the response is inadequate after 3 to 6 injections.<sup>57</sup> An estimated 10% to 25% of patients do not respond adequately to initial treatment.<sup>66,67</sup> Retinal specialists need to be able to access treatment alternatives, as treatment delays are associated with worsened visual acuity.<sup>68</sup> As the third agent to reach the market, aflibercept has been evaluated in patients with persistent disease activity despite treatment with bevacizumab or ranibizumab. In a post hoc analysis of the VIEW trials, patients with early persistent retinal fluid had greater visual gains and less vision loss with aflibercept 2 mg every 4 weeks than with ranibizumab 0.5 mg every 4 weeks or aflibercept 2 mg every 8 weeks.<sup>69</sup> A meta-analysis of 28 studies in more than 2200 eyes found that aflibercept stabilizes vision loss in patients with treatment resistance to bevacizumab or ranibizumab.<sup>67</sup> Pigment epithelial detachment during treatment with bevacizumab or ranibizumab was also found to stabilize after switching to aflibercept.<sup>59</sup>

### Emerging Treatment Options for Age-Related Macular Degeneration

Emerging anti-VEGF treatment options may help to reduce the burden of frequent injections. This can be beneficial for many stakeholders, including patients and their caregivers, overextended ophthalmology practices, and payers. Reducing the burden of anti-VEGF injections may also decrease the risk of rare complications, including endophthalmitis, retinal detachment, and increased intraocular pressure.<sup>34</sup> Results of the 2018 ASRS survey found that the majority US retinal specialists considered the greatest unmet need of patients with nAMD to be a reduced treatment burden (73.2%) followed by long-acting or sustained delivery options (56%).<sup>57</sup> An additional unmet need is the treatment gap with currently available agents. More than half of patients have vision loss that may limit daily activities despite receiving an anti-VEGF agent.<sup>70</sup> This suggests that agents with different mechanisms of action would benefit patient care. Innovative agents in phase 3 clinical development for nAMD are discussed in later sections. This does not include gene therapy as these agents are still in early phases of development.

### Abicipar Pegol

Abicipar pegol (formerly AGN-150998) specifically binds with high affinity to all soluble isoforms of VEGF-A.<sup>71</sup> Properties that may account for the longer duration of action include a longer ocular

half-life, pegylated molecular structure, and high target-binding affinity.<sup>71</sup> Initial results have been reported from 2 phase 3 clinical trials (SEQUOIA and CEDAR) that compared abicipar pegol and ranibizumab in treatment-naïve patients with nAMD.<sup>72</sup> Patients were randomized to 3 arms: abicipar pegol every 4 weeks for 3 doses, followed by every 8 weeks; abicipar pegol every 4 weeks for 2 doses, with a subsequent dose after 8 weeks followed by every 12 weeks; or ranibizumab every 4 weeks. The prespecified primary end point was noninferiority to ranibizumab for stable vision (vision loss of  $\leq 15$  letters in best corrected visual acuity [BCVA] from baseline) at 1 year. The efficacy and the overall AE rate were similar after 1 year of treatment that required 6 to 8 injections of abicipar pegol compared with 13 injections of ranibizumab. However, those treated with abicipar pegol had a substantial incidence of intraocular inflammation, with roughly 15% of abicipar-treated eyes experiencing this AE. The manufacturing process has been modified in an effort to reduce intraocular inflammation with abicipar pegol. The MAPLE Study suggests these efforts have been modestly successful. This follow-up 100-patient study had a reduced intraocular inflammation (IOI) rate of 8.9%, and only 1.6% of the IOI cases were deemed moderately severe or severe.<sup>73</sup>

### Brolucizumab

Brolucizumab (formerly RTH258 and ESBA1008) is a humanized single-chain antibody fragment that inhibits all forms of VEGF-A.<sup>4</sup> A low molecular weight (26 kDa) and high concentration gradient between vitreous and retina may enhance retinal delivery of brolucizumab.<sup>74</sup> Brolucizumab has high stability and solubility, allowing delivery of a higher dose in the usual volume of an intravitreal injection.<sup>4</sup>

Two published phase 3 trials (HAWK and HARRIER) compared brolucizumab with aflibercept in treatment-naïve patients with nAMD.<sup>74</sup> The primary end point in both studies was noninferiority to aflibercept in mean change in BCVA from baseline to week 48. Patients were randomized to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg in HAWK; HARRIER randomized patients to brolucizumab 6 mg or aflibercept 2 mg. After doses at weeks 0, 4, and 8, brolucizumab was given every 12 weeks unless disease activity was found at week 16. After doses at weeks 0, 4, and 8, aflibercept was given every 8 weeks. At week 16, a masked investigator assessed disease activity using specific criteria for central subfield thickness (CST) and intraretinal fluid (IRF) on spectral domain OCT. If disease activity was present, the dosing interval of brolucizumab was permanently reduced to every 8 weeks. During the HAWK trial, a prespecified superiority analysis was conducted at week 16, when both brolucizumab and aflibercept had the same treatment exposure.<sup>74</sup>

Brolucizumab was noninferior to aflibercept in the primary outcomes in both studies.<sup>74</sup> More than half of patients receiving brolucizumab 6 mg continued on the 12-week dosing interval through week 48, a reduction of 2 injections per year. In the prespecified

superiority analysis of HAWK at week 16, the incidence of disease activity was lower with brolucizumab 6 mg compared with aflibercept (24.0% vs 34.5%;  $P = .001$ ). Superiority was also demonstrated for CST reduction and presence of IRF/SRF.<sup>74</sup>

Overall rates of ocular and nonocular AEs were similar with brolucizumab and aflibercept.<sup>74</sup> Uveitis and iritis occurred somewhat more frequently with brolucizumab than aflibercept. The rate of uveitis was 2.2% with brolucizumab 6 mg and 0.3% with aflibercept in HAWK, and  $<1\%$  with both drugs in HARRIER. The incidence of iritis was 2.2% with brolucizumab 6 mg and 0% with aflibercept in HAWK, and  $<1\%$  with both drugs in HARRIER.<sup>74</sup> A biologics license application has been submitted to the FDA. If approved, it could reach the market by the end of 2019.<sup>75</sup>

### Faricimab

Faricimab (formerly RG7716 or RO 6867461) is a bispecific antibody that binds both VEGF-A and Ang-2 with high affinity and specificity.<sup>76</sup> Preliminary data from phase 2 clinical trials suggest that faricimab has the potential to extend the dosing interval to every 16 weeks during maintenance therapy. Phase 3 clinical trials in nAMD, TENAYA and LUCERNE, are currently underway.<sup>77</sup>

### ONS-5010

ONS-5010 is an intravitreal bevacizumab formulation that entered phase 3 development for nAMD in late 2018<sup>78</sup> that is also being evaluated for treatment of diabetic macular edema and branch retinal vein occlusion. Although it met bioequivalency criteria compared with both US and European reference products in a phase 1 trial, ONS-5010 is not being developed as a biosimilar. Two phase 3 trials will be comparing ONS-5010 with ranibizumab. The first trial is currently enrolling patients in Australia and New Zealand, and the second 11-month trial began recruiting 180 patients in the United States in the second quarter of 2019.<sup>79</sup>

### Ranibizumab Port Delivery System

An investigative approach that intends to provide sustained intraocular delivery of an anti-VEGF agent is the ranibizumab port delivery system (PDS).<sup>80,81</sup> The PDS, which is slightly longer than a grain of rice, is implanted through a small incision in the sclera at the pars plana. Insertion occurs in a surgical procedure under local anesthesia. The procedure includes laser ablation of the choroidal vessels at the incision line to reduce the risk of vitreous hemorrhage. After implantation, the PDS continuously releases ranibizumab via passive diffusion into the vitreous cavity. Refilling the port is an office procedure that is slightly more complex than an intravitreal injection. A customized needle, which must be held perpendicular to the device, injects ranibizumab into a self-sealing septum in the center of the implant. The needle has a dual lumen to remove and replace any remaining ranibizumab from the implant.<sup>80</sup>

Published results of the phase 2 LADDER trial provide insights about this approach.<sup>80</sup> After 9 months, patients receiving ranibizumab 100 mg/mL and monthly ranibizumab injections had similar increases in BCVA (adjusted mean change from baseline of +5.0 vs +3.9 letters) and reductions in central foveal thickness. In patients receiving the implant, rates of ocular serious AEs and postoperative vitreous hemorrhage were 8.9% and 4.5%, respectively. The ranibizumab PDS is currently being evaluated in ARCHWAY, a phase 3 clinical trial enrolling patients with recently diagnosed nAMD who have responded to anti-VEGF therapy.<sup>80</sup>

### Intravitreal Anti-VEGF Biosimilars

In addition to the new molecular entities discussed here, managed care will likely need to adapt to the entry of anti-VEGF biosimilars in the market. Patent expiration dates in the United States are in July 2019 for bevacizumab,<sup>82</sup> June 2020 for ranibizumab,<sup>83</sup> and June 2020 for aflibercept.<sup>84</sup> Bevacizumab-awwb (Mvasi), a biosimilar for the treatment of colorectal, lung, brain, kidney, and cervical cancers,<sup>85</sup> received FDA approval in 2017.<sup>86</sup> Patent litigation concerns have prevented bevacizumab-awwb from reaching the US market, but it is forecasted to launch in July 2019.<sup>87</sup> Another bevacizumab biosimilar, SB8, is currently in phase 3 development.<sup>88</sup> It is unclear how bevacizumab biosimilars intended for use in oncology will affect the repackaging of bevacizumab for intravitreal administration by compounding facilities. Any impact may be temporary, depending on whether the FDA grants approval to ONS-5010. Ranibizumab biosimilars in phase 3 development include FYB201, SB11, and Xlucane.<sup>84</sup> Development of FYB201 is on track for FDA approval by the time patents for ranibizumab expire. Aflibercept biosimilars are also in development.<sup>84</sup>

### Management of Neovascular AMD in Managed Care

The cost of providing care to patients with nAMD is a key issue for the Centers for Medicare & Medicaid Services (CMS), as anti-VEGF agents account for a large portion of the CMS budget.<sup>89</sup> In August 2018, CMS released a memo that allows Medicare Advantage plans to implement step therapy for physician-administered part B drugs starting January 1, 2019.<sup>90</sup> A previous 2012 memo had prohibited this practice for Medicare Advantage plans.<sup>91</sup> This policy change has raised awareness among medical organizations that represent retinal specialists and other ophthalmologists that the policy could cause sight-threatening delays in accessing appropriate and necessary anti-VEGF agents, based on clinical judgment. Dialogue between payers and providers about the latest advancements in nAMD management is a key tool in helping to provide optimal and cost-effective healthcare services to patients with this disease. The impact of anti-VEGF agent cost efficacy and other cost- and quality-related issues will be discussed in detail in the second section of this supplement.

### Conclusions

To serve the needs of patients with nAMD, retinal specialists need immediate access to new treatment options with longer dosing intervals due to sustained delivery or increased durability of anti-VEGF drugs. Agents with new mechanisms of action are also needed for patients who do not respond adequately to current anti-VEGF agents. Anti-VEGF agents that address these needs are expected to reach the market over the next few years. Brolucizumab and abicipar pegol are anti-VEGF agents proven to be effective with extended dosing intervals and are expected to be considered for FDA approval sooner than faricimab or ranibizumab PDS. Development of abicipar pegol may be impeded by a high rate of intraocular inflammation. The ranibizumab PDS phase 3 clinical trial (ARCHWAY) is expected to show whether continuous (as opposed to pulsatile with injections) exposure to anti-VEGF therapy can improve the treatment response. Clinical trials with faricimab, the bispecific antibody that binds both VEGF-A and Ang-2, will elucidate the role of Ang-2 in nAMD. FDA approval of ONS-5010, the first bevacizumab formulation designed for intravitreal administration, could eliminate the need for bevacizumab compounding by 503B compounding pharmacies. As clinical development of these agents progresses, optimism is building that patients with nAMD will soon have a lighter burden of injections and monitoring while still maintaining their vision. ■

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