REPORT

Wet Age-Related Macular Degeneration: Treatment Advances to Reduce the Injection Burden

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Introduction

More than 11 million Americans are living with age-related macular degeneration (AMD), an eye disease of elderly individuals that causes a progressive loss of the central vision that is needed to drive, read, recognize faces, and see the world in color.[1] Up to 200,000 Americans are newly diagnosed with AMD each year.[2] According to the World Health Organization, 196 million people have AMD globally, including 10.4 million people with moderate to severe vision impairment or blindness.[3] Due to an aging population, the global burden of AMD is expected to rise to more than 243 million cases in 2030.

AMD-attributed blindness has dropped by approximately 50% to 70% since anti-vascular endothelial growth factor (anti-VEGF) medications were introduced 15 years ago.[4,5] However, anti-VEGF agents may suppress disease neovascular AMD activity just temporarily, and the progression of AMD can be relentless. Patients with neovascular AMD may require monthly clinic visits for costly intravitreal injections for a decade or longer.[6] The chronicity and invasiveness of anti-VEGF therapy can take a substantial toll on patient and caregiver quality of life; all other activities must be planned around time-consuming clinic visits.[7,8] As shown in **Table 1**,[9-13] a myriad of factors can affect adherence to an anti-VEGF treatment regimen.[9-13] Results of real-world studies have recently highlighted that patients with neovascular AMD are often undertreated and, as a result, their visual potential may not be maximized. In one study, about 50% of patients missed clinic appointments while more than 20% had gaps of over 100 days between clinic appointments.[14] Another study found that about 1 in 5 patients were lost to follow-up; this was linked to associated vision loss.[15,16]

In randomized clinical trials, visual acuity on an eye chart was maintained within 3 lines of baseline in 95% or more of patients after 2 years of anti-VEGF injections.[17] Unfortunately, these vision gains were often not maintained after leaving the protocol-driven clinical trial environment.[18,19] Vision preservation in the real world appears to fall short of these clinical trial results, with indications that patients receive fewer anti-VEGF injections and less frequent monitoring than recommended.[20-22] For example, Medicare Part B data

ABSTRACT

The burden of age-related macular degeneration (AMD), a leading cause of vision loss in the elderly population, is poised to increase dramatically as the baby boomer generation ages. Fortunately, the prognosis of neovascular AMD has improved dramatically since anti-vascular endothelial growth factor (VEGF) agents reached the market 15 years ago. In large-scale clinical trials, anti-VEGF utilization maintained visual acuity in more than 90% of patients. However, providing anti-VEGF treatment requires the specialized expertise of retina specialists and is labor intensive and costly. Further, results in clinical practice do not always measure up to those obtained in rigorous phase 3 trials. Undertreatment and the burden on patients and caregivers from frequent anti-VEGF injections contribute to suboptimal visual acuity results in the real world. As a consequence, retinal specialists are focused on finding effective strategies to extend the dosing interval. These include individualized optical coherence tomography–guided dosing regimens, longer acting new agents with similar or new mechanisms of action, and sustained release delivery devices. With the recent approval of brolucizumab, the neovascular AMD armamentarium has expanded to 4 anti-VEGF agents, and more are in development. Understanding the treatment landscape is a key issue in managed care due to the substantial cost of anti-VEGF medications. The goal of this article is to provide managed care clinicians with an up-to-date assessment of currently available agents, followed by a preview of some investigational agents that could alter the future treatment landscape. These agents include abicipar pegol, faricimab, the ranibizumab port delivery system, an intravitreal bevacizumab formulation, and anti-VEGF biosimilars.

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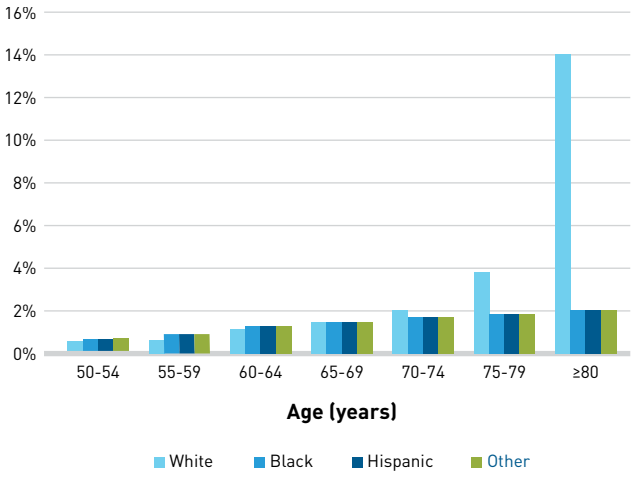
For author information and disclosures, see end of text.

TABLE 1. Factors Linked to Nonadherence With Intravitreal Anti-VEGF Injections[9-13]

- Lack of knowledge about benefits of anti-VEGF therapy
- Loss of mobility
- Lack of transportation
- Fear of injections
- Fear of receiving a poor prognosis
- Comorbid depression or anxiety
- Serious comorbid illness taking priority
- Vacation or travel
- High out-of-pocket costs

VEGF indicates vascular endothelial growth factor.

FIGURE. 2010 US Prevalence Rates for Late Age-Related Macular Degeneration by Race and Age[35]



from 2012 to 2016 indicate that patients received approximately 4.2 injections annually, which is fewer injections than most anti-VEGF regimens require.[23] This is evident when comparing this number with the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) studies, where aflibercept on-label for neovascular AMD would require approximately 14 injections over 2 years.[24] In the 2019 American Society of Retinal Specialists (ASRS) Preferences and Trends Survey, more than 60% of retinal specialists felt that neovascular AMD is undertreated.[25] Addressing undertreatment and the huge injection burden of anti-VEGF therapy are unmet needs of patients with neovascular AMD. This article examines current and evolving approaches to address these needs.

Pathophysiology of AMD: Wet Versus Dry

AMD is characterized by progressive degeneration of the macula, the central part of the retina, leading to central vision loss.[26] AMD can be classified as early, intermediate, or late based on its clinical features, which may include drusen, pigmentation abnormalities, atrophy of the retinal pigment epithelium (RPE), and exudative choroidal neovascularization (CNV). AMD can also be characterized as either dry (atrophic or nonneovascular) or wet (exudative or neovascular). Dry AMD accounts for about 90% of AMD cases but only 10% of AMD-related vision loss.[26] Vision loss from advanced dry AMD often features "geographic atrophy," which is characterized by a sharp border demarcating atrophic areas of RPE from less-affected retinal tissue. Conversely, wet AMD, hereafter referred to as neovascular AMD, accounts for roughly 10% of AMD cases, but almost 90% of AMD-related central vision loss.[26]

In geographic atrophy, the patches of RPE atrophy often start around the fovea with gradual progression over years to the foveal center; this is accompanied by visual loss.[27,28] In a recent clinical trial, patients with bilateral geographic atrophy and no neovascular AMD lost a mean of almost 5 letters in best corrected visual acuity letter score over less than 1 year.[29] Currently, no marketed drugs treat geographic atrophy, although some investigational agents appear promising.[26,30,31] Some concern has been raised that long-term anti-VEGF treatment of neovascular AMD may increase the progression of geographic atrophy, although this has not been demonstrated in clinical studies.[32]

Neovascular AMD is characterized by CNV, which occurs when abnormal leaky blood vessels grow from the choroid into the subretinal space, causing retinal edema, progressive degeneration of photoreceptors and the RPE, and functional deterioration.[26,27] The pathologic process is associated with overexpression of VEGF-A, which induces angiogenesis and increases vascular permeability and inflammation.[33] The VEGF protein family, which includes VEGF-A, -B, -C, and -D; virally encoded VEGF-E; and placental growth factor, regulates retinal vascular permeability. Common symptoms of neovascular AMD include distortion of straight lines (metamorphopsia), a blind spot or hole in one's vision (scotoma), and difficulty with adaptation to the dark.[34] Central vision loss can progress over the course of weeks, even days, in a more rapid fashion compared with dry AMD.[27] Patients with advanced late AMD can have geographic atrophy, neovascular AMD, features of both, or disciform scarring, which is the end-stage result of neovascular AMD.[28]

Epidemiology of AMD

AMD occurs primarily in elderly individuals, with a striking increase in late AMD in those 75 years or older.[35,36] In 2010, the population of those with late AMD in the United States was 89% white, 4% black, and 4% Hispanic.[35] As shown in the **Figure**,[35] the prevalence of late AMD in Caucasian Americans increased from 2% at age 70 years to just under 14% at age 80 years, whereas by age 80 it remained at about 2% in other ethnic or racial groups. The prevalence of AMD is not affected by gender.[36] However, due to longer life expectancy, women account for 65% of late AMD cases in the United States. As

the US population ages, the incidence of late AMD is projected to markedly increase, from 2.07 million in 2010 to 5.44 million by 2050.[35]

A complex interaction between genetics and environmental factors, such as smoking and diet, affects an individual's susceptibility to AMD.[37] AMD is a polygenic disease in which multiple gene variants contribute varying amounts to individual risk. A genome-wide association study identified 52 gene variants that may account for more than 50% of AMD heritability.[38] Smoking is a dose-related risk factor for neovascular AMD, and smoking cessation reduces the risk of AMD progression.[26,39] Twin studies show that environmental factors such as smoking and diet can interact epigenetically with specific gene variants to accelerate the progression of AMD.[37] While early epidemiologic data suggested that aspirin might increase the risk of neovascular AMD, this has been refuted by more recent evidence.[28,40,41] The American Academy of Ophthalmology recommends that patients who have been advised by their physician to take aspirin for a medical indication should continue to take it.[26]

Diagnosis and Monitoring of Neovascular AMD

The clinical diagnosis of AMD is typically made during examination of the retina by an eye care provider.[26,27] Key features include deep RPE pigmentary changes, subretinal fluid or fibrosis, macular edema, and hemorrhage or exudate. Fluorescein angiography can be used to visualize abnormal blood vessels in CNV that leak fluorescein in neovascular AMD. Optical coherence tomography (OCT) provides a cross-sectional image of the retina for detection of subretinal and intraretinal fluid, retinal edema, retinal pigment epithelial detachment, and measurement of retinal thickness.[26,42] Monitoring these structural changes is crucial for evaluating the response to anti-VEGF agents.[26] In the 2019 ASRS survey, retinal specialists ranked the most important OCT features that drive retreatment of neovascular AMD, with more than 92% naming as intraretinal or subretinal fluid and 31% naming sub-RPE fluid.[25] OCT angiography (OCTA) is a novel imaging modality that may be able to detect CNV in neovascular AMD without the need for intravenous injection of dye, such as with fluorescein. OCTA has been able to demonstrate CNV in eyes with dry AMD and may be able to identify eyes that are at higher risk for converting dry AMD to neovascular AMD.[43,44]

Earlier diagnosis, leading to earlier treatment, is critical for patients who convert to neovascular AMD to maintain visual acuity, independence, and quality of life.[26] Patients can lose a mean of 3 to 5 lines of vision in the progression from intermediate to neovascular AMD.[17] Patients with better visual acuity at the start of anti-VEGF therapy are more likely to maintain visual acuity 1 to 2 years later.[45] Patients with neovascular AMD in 1 eye have a substantial risk of developing neovascular AMD in the fellow eye. In a post hoc analysis of the VIEW studies, almost one-third of patients treated for unilateral neovascular AMD had conversion to neovascular AMD in the untreated fellow eye by the end of 2 years of follow-up.[46]

Patient self-monitoring has traditionally been done by periodically checking an Amsler grid for visual distortion.[47] However, a macular visual-field testing method called preferential hyperacuity perimeter (PHP) has much greater sensitivity and specificity for detecting visual distortion.[47] A PHP home monitoring system called ForeseeHome is FDA approved for patients with either intermediate AMD in both eyes, or CNV in 1 eye and intermediate AMD in the other.[48] Telemonitoring transmits patient-collected PHP data to a central data center where the data are analyzed; the patient's retinal specialist is notified if a significant change occurs. In 2018, about 25% of US retinal specialists reported using home PHP monitoring.[49] In 2018, the FDA also approved an app for smartphone or tablet (Alleye) to detect visual distortions in patients with macular diseases such as AMD.[50] Patients measure metamorphopsia with the dot alignment test, and the data are accessible to clinicians via a Web interface.

In December 2018, the FDA granted a breakthrough device designation for an at-home patient self-monitoring OCT device (Home OCT) to monitor neovascular AMD progression between clinic visits.[51] Similar to the PHP monitoring system, patient-collected OCT data are relayed to a cloud-based platform and analyzed with machine learning and an artificial intelligence algorithm. In tests, the device had 90% sensitivity and 100% specificity compared with technician-administered commercial OCT devices.[52] This monitoring system could be available as early as mid-2020.[51]

Current Anti-VEGF Agents

In 2016, more than 690,000 Medicare Part B enrollees received almost 3 million intravitreal anti-VEGF injections.[53] This compares with fewer than 3000 intravitreal injections annually before the "anti-VEGF era," which began in 2004 with the FDA approval of pegaptanib.[54] Additional anti-VEGF agents approved for neovascular AMD include ranibizumab in 2006, aflibercept in 2011, and brolucizumab in 2019. Bevacizumab, which has been used off-label since 2005, remains a treatment option because of its low cost and comparable efficacy.[26,55] Intravitreal anti-VEGF drugs are first-line treatment for neovascular AMD because of their potential to cause robust improvements in vision; they are much more effective in this outcome compared with older treatment options such as photodynamic therapy.[26,34,56,57] Pegaptanib is no longer used because it has less efficacy for vision improvement in clinical trials of neovascular AMD compared with other agents.[26] Laser photocoagulation and photodynamic therapy, considered second-line options, are rarely used today.[26,54] Key properties of current anti-VEGF drugs for neovascular AMD are shown in **Table 2**.[34,58-61]

Treatment decisions in neovascular AMD are informed by the results of comparative trials among anti-VEGF agents.[24,34,58,62-67] Regarding visual acuity, overall efficacy results appear similar for the drugs that have been compared. For example, efficacy between bevacizumab and ranibizumab was comparable in the

TABLE 2. Properties of Anti-VEGF Agents[34,58-61]

	Aflibercept (Eylea)	Bevacizumab (Avastin)	Brolucizumab-dbll (Beovu)	Ranibizumab (Lucentis)
Pharmacology	VEGF-Trap (decoy)	Monoclonal antibody	Single-chain antibody fragment	Antibody fragment
FDA-approved indications	• Neovascular AMD • Macular edema post RVO • DME • DR	Not FDA approved for ophthalmic use	• Neovascular AMD	• Neovascular AMD • Macular edema after RVO • DME • DR • Myopic CNV
Dosing intervals for neovascular AMD	Loading dose of 3 injections at 4-wk intervals, then q8wk dosing. Some patients may need q4wk dosing.	1.25 mg q4wk, based on literature	Loading dose of 3 injections at 4-week intervals, then q8wk to q12wk	0.5 mg q4wk

AMD indicates age-related macular degeneration; CNV, choroidal neovascularization; DME, diabetic macular edema; DR, diabetic retinopathy; PlGF, placental growth factor; q, every; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

Comparison of AMD Treatment Trial (CATT), the Inhibition of VEGF in Age-related Choroidal Neovascularization trial, and the Groupe d'Étude Français Avastin versus Lucentis dans la DMLA Néovasculaire trial.[62-66] Aflibercept and ranibizumab were comparable for maintaining vision (loss of <15 letters) in the VIEW 1 and VIEW 2 trials.[24] Most recently, brolucizumab was noninferior to aflibercept in the HAWK and HARRIER trials.[58,67] Head-to-head trials have not compared bevacizumab versus aflibercept, or brolucizumab versus bevacizumab or ranibizumab. There may be differences among anti-VEGF agents in terms of resolution of fluid on OCT and durability of anti-VEGF effect in an individual patient. While it is not clear what produces individual variations in response to anti-VEGF agents, hypotheses such as anti-VEGF resistance and tachyphylaxis have been explored.[68]

Brolucizumab, the newest agent in clinical use, was designed by grafting the complementarity-determining regions of a novel anti–VEGF-A antibody onto a human single-chain antibody fragment.[67] Due to a higher molar concentration and greater solubility, more molecules of brolucizumab are delivered in the usual volume of an intravitreal injection than are molecules of other anti-VEGF agents.[69,70] In a preclinical study, brolucizumab had 2.2-fold greater retinal exposure and 1.7-fold higher RPE exposure than ranibizumab. It has been suggested that these properties may lead to more rapid, sustained retinal penetration.[67] Ongoing phase 3 trials are evaluating brolucizumab for the treatment of diabetic macular edema and retinal vein occlusion.[71] It is currently available in vials, with a prefilled syringe in development.[71] In February 2020, the American Society of Retinal Specialists issued a note to its members regarding 14 cases of retinal vasculitis in patients receiving brolucizumab. Of these 14 cases, 11 were occlusive retinal vasculitis, which can lead to vision loss. The safety of brolucizumab continues to be studied.[72]

In the HAWK and HARRIER studies, aflibercept and brolucizumab were each given as 3 monthly loading doses followed by a dose every 8 weeks (aflibercept) or 12 weeks (brolucizumab).[67] If disease activity was detected at week 16, the dosing interval of brolucizumab was reduced to every 8 weeks. More than half of patients receiving brolucizumab 6 mg continued with 12-week dosing through week 48, reducing by 2 the annual number of injections. Eyes with no disease activity during the first 12-week dosing interval had a greater than 80% probability of continuing a 12-week dosing interval until week 48. Of key importance to retinal specialists, brolucizumab outperformed on secondary "dryness" end points: central subfield retinal thickness, subretinal fluid, and disease activity. In a prespecified superiority analysis of HAWK, the incidence of disease activity at week 16 was lower with 6 mg brolucizumab than aflibercept 2 mg (24.0% vs 34.5%; $P = .001$). Although overall adverse effect rates were similar between brolucizumab and aflibercept, uveitis and iritis were slightly more frequent with brolucizumab.[67]

The 8-week maintenance dosing interval of aflibercept in HAWK and HARRIER reflects the dosing in VIEW 1/2 studies but may not reflect current real-world usage, where the dosing interval can range from 4 to 12 weeks.[60] A study is being planned that may address this. The TALON study will compare brolucizumab and aflibercept in an identical "treat-to-control" regimen of loading doses at weeks 0, 4, 8, and 16, followed by a dosing interval as long as 16 weeks.[71] Results are expected by mid-2022. The 2019 ASRS survey found that 50% of clinicians intend to use brolucizumab for patients with an incomplete response to other agents.[25] The ongoing phase 3 MERLIN trial is comparing brolucizumab with aflibercept given every 4 weeks in patients with persistent subretinal or intraretinal fluid despite frequent anti-VEGF treatment.[73] Results are expected in late 2020.

Anti-VEGF Treatment Approaches to Reduce the Injection Burden

The goals of anti-VEGF therapy in neovascular AMD are to achieve excellent functional visual acuity and maintain a dry macula on

clinical and OCT examination. This may require an individualized approach because AMD is a heterogenous disease.[74] Although anti-VEGF agents appear effective and somewhat equivalent in large-scale clinical trials, individual patients may respond differently to different drugs. The duration of VEGF suppression appears to vary between drugs as well as with individualized patient responses.[74] For example, disease activity can be suppressed with an injection interval of 10 to 12 weeks in 10% to 20% of patients at one end of the spectrum while a 4-week interval is needed for 10% to 20% of patients at the opposite end.[6]

Two approaches—treat-and-extend (T&E) and pro re nata (PRN; as needed)—have been used to reduce the injection burden in stable, nonexudative patients with neovascular AMD. Pros and cons are compared in **Table 3**.[42] The T&E regimen gradually extends the dosing interval in 2-week increments to a maximum interval of 12 to 16 weeks.[42] If disease activity is observed, then the treatment interval is reduced, often in 2-week increments but this varies with patient treatment factors.

In the PRN regimen, the patient must still comply with monthly OCT monitoring, but an injection is delayed unless warranted by signs of recurrent disease activity.[42,74] To avoid risking vision loss with the PRN regimen, patients must adhere to frequent, potentially monthly, monitoring visits while clinicians adhere to prespecified objective OCT retreatment criteria.[75] The pros and cons of PRN dosing are illustrated by 2-year data from CATT.[63] The mean visual acuity gain with PRN bevacizumab or ranibizumab was 2.4 letters less than monthly dosing of either drug ($P = .046$). But the decrement in vision gain was accompanied by a much lower injection burden. Patients receiving monthly ranibizumab or bevacizumab received a mean of 22.4 or 23.4 injections, respectively, whereas patients receiving PRN ranibizumab or bevacizumab received 12.6 or 14.1 injections. Some retinal specialists consider the PRN approach for patients at high risk for geographic atrophy because it minimizes anti-VEGF agent exposure, a potential driver of geographic atrophy.[42,76] In the 2015 ASRS survey, almost 65% of US retinal specialists preferred a T&E regimen.[6] In 2019, more than 60% preferred giving at least 3 monthly loading injections before using a T&E regimen and about 20% preferred a T&E regimen after the retina is dry or stable without loading doses.[25]

Recently published 1-year data from 2 clinical trials provide more insights into T&E regimens. The Canadian Treat-and-Extend Analysis Trial with Ranibizumab study compared ranibizumab given monthly versus ranibizumab T&E after 3 monthly doses.[77] At 1 year, T&E ranibizumab was noninferior to monthly dosing for visual acuity, but it required a mean of 2.46 fewer injections (9.4 vs 11.8 injections; $P < .001$). In the T&E arm, the treatment interval was 8 weeks or greater in almost 70% of patients and 12 weeks or greater in almost 30% of patients.[77] The Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in (Wet) AMD Patients study compared identical T&E regimens of aflibercept and ranibizumab.[78] At 1 year, there was no difference between the 2 drugs in visual acuity improvement or the mean number of injections given (9.7 injections). The primary end point of the study, the mean change in area of macular atrophy from baseline to 2 years, has not been reported yet. A retrospective analysis of 3-year data from the Fight Retinal Blindness! Project, a prospectively designed observational outcomes registry, also reported that visual acuity and the number of clinic visits and injections was similar with aflibercept and ranibizumab T&E regimens.[79]

TABLE 3. Treat-and-Extend Versus As-Needed Dosing Interval Extension[42]

	Treat-and-Extend	As-Needed
Approach	Increase dosing interval in 2-week increments to maximum of 12-16 weeks	Monitor closely and give next dose after disease activity is detected
Pros and Cons	• More proactive for preventing vision loss • Geographic atrophy risk may be increased	• Risk of disease activity and potential vision loss may be higher • Close monitoring is required

Emerging Treatment Options

A robust pipeline of investigational drugs for neovascular AMD is expected to extend the dosing interval beyond that of currently available agents. Agents that are expected to reach the market within the next 3 years include abicipar pegol and faricimab, as well as the ranibizumab port system for extended-release drug delivery. An intravitreal bevacizumab formulation and anti-VEFG biosimilars are also expected to change the treatment landscape. Further out on the horizon, gene therapy could be another option for addressing the anti-VEGF injection burden.

Abicipar pegol. This novel agent was engineered with designed ankyrin repeat proteins (DARPin) technology to have both a longer ocular half-life and rapid systemic clearance.[80] DARPin technology uses a library of single-domain proteins to build multifunctional protein-binding molecules.[81,82] Abicipar pegol has a molecular weight of 34 kDa.[83] In vitro VEGF-A_{165} binding affinity of abicipar pegol was similar to that of aflibercept and greater than that of ranibizumab and bevacizumab. In the phase 3 SEQUOIA and CEDAR clinical trials, treatment-naïve patients with neovascular AMD received abicipar pegol at weeks 0, 4, 8, and then every 8 weeks; or abicipar pegol at weeks 0, 4, 12, and then every 12 weeks; or ranibizumab every 4 weeks.[84] For both the 8- and 12-week dosing regimens, abicipar pegol met the prespecified primary end point of stable vision that was noninferior to monthly ranibizumab after 1 year of treatment. After 2 years of treatment, visual gains and CRT results were comparable for monthly ranibizumab and quarterly injections of abicipar.

Abicipar pegol required fewer injections than ranibizumab in the first year (6-8 vs 13) and the second year (4 vs 12).

In the first year of SEQUOIA and CEDAR, the rate of intraocular inflammation (IOI; uveitis or iritis) ranged from 15.1% to 15.7% in abicipar pegol treatment groups versus 0% to 0.6% with ranibizumab.[82] Although most cases were reportedly mild, 3.5% of abicipar pegol–treated patients had severe IOI.[85] In the second year, the pooled rate of new cases of IOI was 1.9% for abicipar pegol versus 1% for ranibizumab.[84] After impurities were found in the formulation that may have come from *Escherichia coli* fragments (a byproduct of the manufacturing process), the company modified the manufacturing process to reduce the risk of IOI.[82] In the follow-up MAPLE study with a smaller sample size, the overall incidence of IOI and severe IOI was 8.9% and 1.6%, respectively. A Biologics License Application for abicipar pegol was submitted to the FDA in September 2019. The agency is expected to act on it by mid-2020.[84]

Faricimab. This novel bispecific antibody binds both VEGF-A and Ang-2 with high affinity and specificity. Upregulation of Ang-2 is thought to drive vessel destabilization and inflammatory signaling in neovascular AMD.[86] The Fc portion of the antibody was modified to minimize systemic exposure and inflammatory effects.[86,87] Results of the phase 2 STAIRWAY clinical trial suggest that faricimab can extend the dosing interval to 16 weeks during maintenance therapy of neovascular AMD.[86,88] In this study, patients were randomized to flexibly dosed faricimab at every 16 weeks, faricimab every 12 weeks, or ranibizumab every 4 weeks. Visual acuity outcomes were similar for the 3 study arms, with a mean increase in chart letters of 11.4, 10.1, and 9.6 letters, respectively. All 3 regimens were similar in the proportion of patients gaining more than 15 letters and avoiding loss of more than 15 letters. Comparable reductions in central retinal thickness also were reported in all 3 arms. Ocular and systemic adverse effects were similar in all groups. Two identical phase 3 clinical trials, TANAYA and LUCERNE, will compare faricimab given every 16 weeks (with the option to decrease to doses every 12 or 8 weeks) with aflibercept given every 8 weeks. Faricimab is also in phase 3 development for diabetic macular edema (DME).[89] An FDA filing for faricimab could occur as early as 2021 for DME and 2022 for neovascular AMD.[89]

Ranibizumab port delivery system (PDS). The PDS is a drug delivery device implanted into the eye that is designed for continuous extended release of ranibizumab via passive diffusion into the vitreous cavity.[89,90] It is inserted through an incision in the sclera at the pars plana in an operating-room procedure performed with local anesthesia. During the procedure, choroidal vessels at the incision line are ablated with a laser to reduce the risk of postoperative vitreous hemorrhage. Refilling the port is an office procedure in which a customized dual lumen needle simultaneously removes and replaces any remaining ranibizumab from the implant.[90] In the phase 2 LADDER trial, eyes treated with the ranibizumab PDS had similar gains in visual acuity and reductions in central foveal thickness compared with eyes treated with monthly ranibizumab injections at 9 months.[91] For ranibizumab PDS eyes, 80% of patients did not require a PDS refill for 6 or more months, and the median time to first required PDS refill was 15 months. In the ongoing phase 3 ARCHWAY clinical trial, the ranibizumab PDS is dosed every 24 weeks in patients with recently diagnosed neovascular AMD that has responded to anti-VEGF therapy.[88,90] An FDA filing for the device is anticipated in 2021.[89]

Conbercept. This antibody is a VEGF decoy protein (molecular weight of 143 kDa) like aflibercept.[91] Incorporation of the fourth binding domain from VEGF 2 appears to increase its VEGF binding capacity and extend the intraocular half-life.[91,92] Intravitreal conbercept was approved to treat neovascular AMD in China in 2013 and is now in phase 3 development in the United States. The phase 3 PANDA-1 and PANDA-2 trials are comparing maintenance doses of conbercept every 8 or 12 weeks with aflibercept every 8 weeks.[93,94] Results are expected in 2022.

ONS-5010. This intravitreal bevacizumab formulation is in clinical development for neovascular AMD, DME, and branch retinal vein occlusion.[95] It is not being developed as a biosimilar. Two ongoing phase 3 clinical trials are comparing monthly doses of ONS-5010 with a ranibizumab regimen of 3 monthly doses followed by quarterly doses. Results of these studies are expected in the second half of 2020. The company anticipates that ONS-5010 could receive FDA approval in 2021 or 2022.[95] FDA approval of ONS-5010 could significantly alter the treatment landscape for neovascular AMD. Twelve years of marketing exclusivity is expected to provide patent protection from bevacizumab biosimilars.[95] Furthermore, with an FDA-approved product on the market, 503B compounding facilities would be prohibited from repackaging antineoplastic bevacizumab into syringes.[96] The practice of compounded bevacizumab has provided a low-cost treatment alternative for neovascular AMD, although it has also been linked to variable bevacizumab concentrations, silicone oil droplets, and rare clusters of noninfectious and infectious endophthalmitis.[50,97-99]

Anti-VEGF biosimilars. In July 2019, the first antineoplastic biosimilar for bevacizumab (Mvasi) reached the US market at a wholesale acquisition cost 15% lower than that of the reference biologic.[100] Whether compounding facilities will repackage bevacizumab antineoplastic biosimilars for intravitreal administration is unclear. Biosimilars for ranibizumab and aflibercept are expected to reach the US market after ranibizumab and aflibercept patents expire in June 2020 and November 2023, respectively.[101,102] Ranibizumab biosimilars in late-stage clinical development include FYB201 (Formycon and Bioeq), SB11 (Samsung Bioepis), and Xlucane (Xbrane Biopharma).[103-105] FYB201 met the primary end point in the phase 3 COLUMBUS-AMD clinical trial comparing it with the

reference biologic (Lucentis).[104] An FDA submission for FYB201 was submitted in the last quarter of 2019, with approval expected in 2021. Aflibercept biosimilars are in phase 3 clinical development.[103,104]

Gene therapy. Initial clinical data for gene therapy have generated cautious excitement about its potential to substantially reduce the treatment burden in neovascular AMD. The technology uses a viral vector to insert the DNA coding sequence for an anti-VEGF agent into retinal cells that then act like anti-VEGF factories. In the phase 1 OPTIC clinical trial of ADVM-022, 6 patients who received a single injection of ADVM-022 did not require additional anti-VEGF treatment over 6 months of follow-up.[106] Before the study, these patients had received a mean of 35 anti-VEGF injections. ADVM-022 has received a fast-track designation from the FDA. Submission of a new drug application is expected in the first half of 2020. RGX-314 is another vector-delivered anti-VEGF antibody fragment in phase 1/2 clinical trials that has also shown promise for reducing the injection burden in neovascular AMD.[107]

Conclusions

Minimizing the monitoring and injection burden is an important unmet need of patients with neovascular AMD. The recent approval of brolucizumab adds another anti-VEGF agent and future options expand the mechanistic approach. Managed care professionals should anticipate that the therapeutic landscape in neovascular AMD will become much more crowded and complex over the next few years. Potential entrants include abicipar pegol in 2020; a ranibizumab biosimilar in 2021; and ONS-5010, faricimab, and the ranibizumab PDS in 2021 or 2022. In addition to extending the dosing interval, the ranibizumab PDS phase 3 clinical trial will show whether continuous anti-VEGF exposure can improve the treatment response over that of periodic injections. Likewise, phase 3 trials of faricimab will show whether dual targeting against Ang-2 and VEGF can improve treatment efficacy in neovascular AMD. With gene therapy and home OCT monitoring on the horizon, paradigm shifts seem to be the rule rather than the exception in neovascular AMD management. ■

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