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Improving Treatment Strategies for Wet Age-Related Macular Degeneration

HIGHLIGHTS

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Improving Treatment Strategies for Wet Age-Related Macular Degeneration

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Pharmacists and managed care professionals

Activity Overview

Age-related macular degeneration (AMD), an eye disease with an onset in later life, is a leading cause of visual impairment and blindness both in the United States and around the world. Over the past 15 years, intravitreal anti-vascular endothelial growth factor (VEGF) agents have revolutionized the management of neovascular AMD. Improvements in vision preservation and quality of life come with a cost: regular office visits for monitoring and for intravitreal anti-VEGF injections, and financial strain. This activity will enable managed care pharmacists to have a better understanding of new treatment modalities and strategies to optimize treatment in neovascular AMD.

Statement of Educational Need

More than 11 million Americans are living with age-related macular degeneration (AMD), an eye disease of the elderly population that causes a progressive loss of the central vision that is needed to drive, read, recognize faces, and see the world in color. AMD can progress quickly, with vision deteriorating within days of clinical manifestation. Over the past 15 years, intravitreal anti-vascular endothelial growth factor (VEGF) agents have revolutionized the management of neovascular AMD. Based on clinical trial data, at least 95% of patients are expected to remain within 3 lines of their baseline visual acuity after 2 years of treatment with an anti-VEGF agent; however, vision preservation in the real world falls short of clinical trial results. Some patients will continue to require monthly anti-VEGF injections after 10 years of treatment, which can threaten adherence. Medicare shoulders the burden of paying for neovascular AMD, and rising costs of drug therapy must be considered along with the growing demand for treatment. Continuing education will improve managed care professionals' and pharmacists' competency in managing AMD through a greater insight into the new treatment modalities and strategies to optimize treatment.

Educational Objectives

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

- Outline the epidemiology, pathophysiology, and disease burden of neovascular AMD and explore the impact of technological advancements in AMD diagnosis and monitoring.
- Examine clinical efficacy and safety, dosage regimens, and unique attributes of current and emerging anti-VEGF agents for neovascular AMD.
- Identify anti-VEGF treatment regimens that minimize the injection burden in neovascular AMD.
- Explore factors that affect the delivery of cost-effective therapy to patients with neovascular AMD.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of advances in treatment of wet age-related macular degeneration, including the potential cost implications of new treatment modalities.

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FACULTY

Caroline R. Baumal, MD
Professor
Tufts University School of Medicine
Boston, Massachusetts

Winston Wong, PharmD
President
W-Squared Group
Longboat Key, Florida

MEDICAL WRITING & EDITORIAL SUPPORT

Jill E. Allen, PharmD, BCPS
Medical Writer and Drug Information Consultant
Pin Oak Associates
Salt Lake City, Utah

Elizabeth Paczolt, MD, FACNM
Consultant Medical Writer/Director
Churchville, Pennsylvania

FACULTY DISCLOSURES

Caroline R. Baumal, MD, has the following relevant financial relationships with commercial interests to disclose:
Consultancies or paid advisory boards: Genentech, Novartis, Ocular Therapeutics
Lecture fees: Genentech, Novartis, Zeiss.

Winston Wong, PharmD, has no relevant financial relationships with commercial interests to disclose.

MEDICAL WRITING & EDITORIAL SUPPORT DISCLOSURES

Jill E. Allen, PharmD, BCPS, and **Elizabeth Paczolt, MD, FACNM,** have no relevant financial relationships with commercial interests to disclose.

The American Journal of Managed Care®

Publishing Staff: Ida Delmendo, Ted Pigeon, Angelia Szwed, Monica Tran, Elizabeth Kukielka, and Andrea Szeszko have no relevant financial relationships with commercial interests to disclose.

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Planning Staff: Jim Palatine, RPh, MBA; Maryjo Dixon, RPh; Kimberly Simpson, PharmD; Olivia Mastrodonato; Susan Pordon; and Brianna Winters have no relevant financial relationships with commercial interests to disclose.

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REPORT

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

Caroline R. Baumal, MD

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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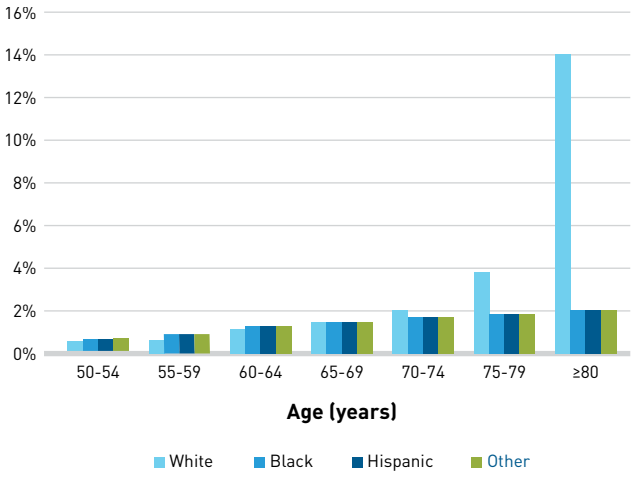
For author information and disclosures, see end of text.

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. ■

Author affiliation: Caroline R. Baumal, MD, is a professor at Tufts University School of Medicine and a vitreoretinal surgeon at New England Eye Center, both in Boston, MA.

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Address correspondence to: cbaumal@tuftsmedicalcenter.org.

Medical writing and editorial support: Jill E. Allen, PharmD, BCPS.

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Managed Care Opportunities and Approaches to Select Treatment for Sight Preservation

Winston Wong, PharmD

ABSTRACT

Neovascular (or wet) age-related macular degeneration (AMD) affects more than 10% of people older than 65 years in North America, Europe, Australia, and Asia. It is estimated that about 11 million Americans have some form of AMD, with that number expected to double by 2050. Approximately 20% of patients will advance from a nonneovascular form of the disease to neovascular AMD, which is associated with central visual acuity loss that can result in severe visual impairment and blindness. Improvements in vision preservation and quality of life require regular clinical visits for intravitreal therapy, which, while effective, come at high cost and potential financial strain, often complicated by the fact that most patients with the disease will be covered by Medicare and subject to the regulations and restrictions within their insurance plans. The requirement for frequent treatment also threatens adherence to therapy, and many patients do not follow up clinically as advised. The confluence of high-cost drug therapy and growing demand for treatment of a sight-threatening disease creates a mandate that managed care professionals and payers focus on current and emerging management options in neovascular AMD and on how to administer therapies in both a clinically responsible and cost-effective manner to diminish risk of vision loss and improve overall patient outcomes.

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For author information and disclosures, see end of text.

The Burden of AMD

Impact on Patient Quality of Life

As a patient's visual function deteriorates with progressive AMD, their quality of life (QOL) also declines in a parallel fashion.[1-3] Decrements in QOL associated with visual disability in neovascular AMD can be as severe as seen in other diseases, such as renal failure or stroke.[4] In an early study, the degree of vision loss in patients with AMD was quantified and correlated with their decline in QOL. A mild visual acuity deficit was associated with a 17% decline in QOL. A moderate visual acuity deficit was associated with a 32% decline in QOL, similar to that seen with severe angina or a hip fracture. Patients with severe visual acuity deficit experienced a 53% decline in QOL, more than that seen in patients undergoing hemodialysis. Very severe loss of vision correlated to a 60% decline in QOL, similar to that seen in patients with end-stage prostate cancer or a catastrophic stroke that had left them bedridden and needing continual medical care. Importantly, patients with varying degrees of disease severity were found to experience QOL impairment that ranged from 96% to 750% greater than the damage estimated by the ophthalmologists treating their AMD.[1,5] Loss of visual acuity also increases the risk of falls and subsequent injury. With increasing loss of visual function, activities of daily living, including basic activities like meal preparation, grocery shopping, and out-of-home travel, may be markedly negatively impacted.[3,6] Diminished ability to perform activities of daily living and the number of relinquished activities related to AMD progression have been linked to impairment in cognitive functioning.[3,6,7] One in 7 patients with AMD has demonstrated cognitive decline. Following severe central vision loss, depression and visual hallucinations (Charles Bonnet syndrome) can occur.[8] Patients with AMD have also demonstrated increased risk for depression versus patients without the disease. One study found that 44.4% of patients with AMD had clinically significant depressive symptoms and that AMD was independently associated with depressive symptoms that both directly and indirectly reduced general health and social functioning.[3,9] Results of a more recent study showed a 24% prevalence of depression among patients with AMD, with the odds

of a patient having depression or anxiety 1.3 times higher than patients without AMD.[10]

Patient-Centered Outcomes in AMD

In terms of treatment and AMD management, the outcomes that patients with AMD value most must be taken into consideration to improve their overall QOL and functioning. Results of data gathered by the Angiogenesis Foundation showed that the following treatment outcomes were most valued by patients with neovascular AMD[5]:

- **Interpersonal relationships:** Loss of vision compromises and changes a patient's relationships with family and friends.
- **Identity and independence:** Patients with neovascular AMD often state that the disease has cost them their identity and sense of purpose.
- **Safety:** With diminishing vision, personal safety becomes more problematic.
- **Financial stability:** Vision loss associated with neovascular AMD may lead to a significant decline in a patient's economic resources.
- **Measuring functional vision in terms of QOL:** Patients want to mainly retain 3 vision-related functions: reading comprehension, depth perception, and facial recognition. Actual data on patient-reported outcomes vary, including the types of analysis and scoring used in individual studies; however, patient-reported outcome measures (PROMs) are being increasingly emphasized in clinical research. One recent study by Jelin et al explored outcomes in self-reported visual function, symptom status, general health, and satisfaction of treatment in patients with neovascular AMD. Results indicated that both self-reported visual function and symptom state significantly improved following 12 months of intravitreal anti-vascular endothelial growth factor (VEGF) treatment, with treatment including better-seeing eye and best-corrected visual acuity of the treated eye as main predictors of outcome. Overall, increased use of PROM tools in the future as part of a multimodal approach to neovascular AMD management could potentially improve understanding of how the disease and related therapy actually affect patients, and it could also reinforce a focus on patient-centered care.[11]

Compliance and Adherence to Therapy

Another conundrum that clinicians often face in optimal management of patients with neovascular AMD is limited compliance and adherence to prescribed therapy. Data have borne out the negative impact of noncompliance and nonadherence. One study assessing factors influencing compliance with therapy followed patients receiving anti-VEGF injections, in whom treatment consisting of 3 consecutive monthly injections with monthly follow-up thereafter. At 1 year, 39.8% of the patients who completed therapy were found to be unable to fully comply with the pro re nata (PRN; as needed) regimen. Key factors associated with increased compliance included better visual acuity at baseline, smaller lesion size, living closer to the treatment location, higher education and sociocultural status, and greater financial status. The most frequent reasons cited by patients for discontinuing therapy were fear of injection, lack of belief in treatment effectiveness, financial limitations, switching to another site for treatment, and comorbidities beyond AMD.[12] Results of data from patient/caregiver surveys performed by the Angiogenesis Foundation showed that despite long-term studies indicating that regular monthly or every-other-month treatments lead to best outcomes, more than 20% of patients were getting injections fewer than 6 times annually. In addition, 34% admitted to missing an injection, and among those patients, 23% lost vision.[5] Another study by Obeid et al assessed 9007 patients treated for neovascular AMD from 2012 to 2016 in a multistate US practice for loss to follow-up (LTFU). Using an LTFU criterion of a patient having no follow-up within 1 year after at least a single anti-VEGF injection, results demonstrated that 2003 (22.2%) of the patients studied had at least 1 LTFU episode. Factors associated with LTFU included older age, lower regional adjusted gross income, longer distance to the therapy site, and requiring injections in just 1 eye. There were also racial and ethnic differences cited, including higher LTFU rates in both Asian and African American patients.[13,14] These findings emphasize the need for clinicians to pay greater attention to the patient to better understand the complicated dimensions of each individual who needs therapy, to explain the seriousness of the disease as clearly as possible, to identify barriers to seeking care, and to motivate patients to follow up appropriately.[14]

Economic Impact of AMD

Direct and Indirect Medical Costs

The ultimate cost associated with AMD and other optical diseases is visual impairment. This impairment negatively impacts the patient with the disease as well as caregivers and society as a whole. In addition to the clinical consequences, the economic consequences of visual impairment can be substantial.[15] An assessment by Köberlein et al of 22 interventional, noninterventional, and cost-of-illness studies was performed to quantify the direct costs, indirect costs, and intangible effects associated with both visual impairment and legal blindness. Data were obtained from studies performed within the United States and other countries, including Canada, Australia, France, Germany, and the United Kingdom. Results demonstrated that hospitalization, medical services surrounding the visual impairment diagnosis, and therapy were the primary drivers of direct medical costs. Assistive devices and aids, necessary home modifications, and other services, including in-home nursing or assisted living/nursing home placement, were the main factors for

direct nonmedical costs. Overall costs for support services and assistive devices increased as a patient's vision deteriorated. The mean annual expenses per patient identified in terms of US purchasing power parities ranged from $12,175 to $14,029 for patients with moderate visual impairment; $13,154 to $16,321 for those with severe visual impairment; and $14,882 to $24,180 for blindness, which was almost twice that seen for nonblind patients. Caregiver hours and effort correlated to the degree of visual impairment. Caregiver time ranged from 5.8 hours per week for a person with a visual acuity of more than 20/32 to 94.1 hours per week for patients with more severe visual impairment (visual acuity of 20/250 or worse).[15,16]

Impact on Medicare Spending

Costs associated with neovascular AMD are greater than those seen with earlier disease stages (ie, dry AMD). A study of Medicare data used to assess the costs of disease progression to neovascular AMD found that total costs for these patients were approximately double that of controls and also 30% higher than costs for patients with dry AMD. Over a 10-year period, average annual Medicare expenditures increased from $11,265 to $24,494 for patients without progressive disease versus $11,712 to $34,308 for those whose disease had progressed. When ophthalmic expenditures were taken into account, costs for those with neovascular AMD were found to be at least 5-fold higher than for those with dry AMD (range of 4.5 to 9 times higher).[17,18]

Any discussion about the cost of care essentially revolves around Medicare because of the age demographic for neovascular AMD and the fact that Medicare is the primary payer for anti-VEGF therapy.[15] A pivotal study by Day et al assessed a sample of Medicare beneficiaries in 1994, 2000, and 2006 with new diagnoses of neovascular AMD. First-year healthcare and eye care costs were calculated for each beneficiary in the 5% sample. The number of beneficiaries with newly diagnosed neovascular AMD was 2 times higher in 2006 compared with 1994. Overall, yearly Part B payments per beneficiary showed a substantial increase from $3567 for the 1994 group to $5991 for the 2006 group, measured in constant 2008 dollars. Eye care payments alone more than doubled from $1504 in 1994 to $3263 for patients in 2006. It is critical to note that the increase in payments for eye care in 2006 strongly reflected payments for anti-VEGF injections, which were estimated at $1609 over a 1-year period. In addition, the mean annual numbers of both clinical visits and imaging studies were also found to increase considerably between the 1994 and 2006 cohort. Overall, the development of anti-VEGF therapies provided important clinical benefits for patients with neovascular AMD; however, these benefits must be weighed along with the significantly increased costs of providing care for these patients.[19] Data highlight how much the use of anti-VEGF agents has grown over the past 2 decades, with Medicare payments for physician services associated with the administration of anti-angiogenic drugs. Physicians reported 3000 Medicare-covered intravitreal injections in 2000. By 2008, this number had grown to 1 million, and, in 2013, Medicare paid for 2.5 million intravitreal injections. The cost for these injections was estimated at more than $300 million.[15,20]

Patient Out-of-Pocket Cost Issues

Most patients with neovascular AMD are 65 years and older and are Medicare beneficiaries who must cover 20% of allowable reimbursement for anti-VEGF therapy and associated physician administration charges out-of-pocket (OOP). Aside from circumstances when the agent bevacizumab is used, OOP expenses can be considerable and can accumulate quickly for patients with neovascular AMD. With such a heavy cost impact, managed care professionals and payers must become better aware of the demographics surrounding patients with neovascular AMD who are covered by their organization.[15]

Cost Efficacy of Anti-VEGF Strategies

Although the main focus of clinicians is to provide optimal care to maximize clinical outcomes, these outcomes must also be balanced with the cost of care. Payers are responsible both for providing access to high-quality healthcare services and for controlling costs. In doing so, they encounter 2 main barriers to healthcare management. First, they are not always familiar with the scoring metrics used in clinical trials to measure disease activity or progress. Second, it can be a challenge for payers to apply clinical trial data to real-world patient populations, because the inclusion criteria for a trial frequently do not match or correlate to real-world patient populations and clinical practice.[21]

Treatment Option Costs

Of significant importance now in real-time clinical practice is that CMS announced that Medicare Advantage (MA) plans would be able to apply step therapy for physician-administered agents and other Medicare Part B drugs as of January 1, 2019.[22] Step therapy mandates that more cost-effective therapies be used initially before more-expensive alternative agents in a stepwise fashion. Failure of the less expensive drug must occur before the patient can be switched to a more expensive option.[23] This policy change has raised concern among clinicians, especially retina specialists, about potential delayed access to more-expensive anti-VEGF agents for patients with neovascular AMD that could result in sight-threatening outcomes. In the setting of MA plans, concerns center on what exactly will constitute a treatment failure for a particular plan.[24]

Because of the importance of cost containment and these new Medicare factors, clinicians must pay greater attention to both the cost and overall value of anti-VEGF options for neovascular AMD. The AMD treatment market was estimated to be $7.1 billion in 2017, likely increasing to $11.1 billion by 2023.[25] Managed care professionals and payers should estimate how the increasing numbers of patients with AMD will impact their organizations. Additional

issues that organizations must take into consideration include allowable reimbursement versus acquisition cost, drug rebates and purchasing discounts, taxes on gross or drug revenue, and the expected growth in intravitreal injections that will likely occur as the population with AMD ages and grows.[15]

Currently, there are 3 FDA-approved anti-VEGF agents for treatment of neovascular AMD. These include previously approved aflibercept and ranibizumab, which are now joined by brolucizumab, approved in October 2019.[15,26] In addition, bevacizumab is frequently used off-label for therapy in these patients despite its lack of FDA approval for this indication; however, a recent report from the American Academy of Ophthalmology noted that there are now data from prospective, randomized trials that demonstrate the noninferiority of bevacizumab to FDA-approved ranibizumab.[27,28]

Annual American Society of Retina Specialists survey responses provide insight into how retina specialists view anti-VEGF agents with respect to costs. In 2018, the anti-VEGF drug for neovascular AMD used most often in the first-line setting was bevacizumab (70%), followed by aflibercept (16%) and ranibizumab (13%).[29] In 2019, when asked which anti-VEGF drug they would primarily use for new-onset neovascular AMD if cost were not a factor, they listed aflibercept (78%), followed by ranibizumab (14%) and bevacizumab (8%).[30]

Formulary selection and management of anti-VEGF agents is a critical factor in patient management, but managed care professionals and payers have been given minimal guidance from professional organizations on how to incorporate cost into these processes to help determine optimal treatment strategies.[15] A key issue in the treatment of neovascular AMD is that although bevacizumab does not carry an FDA-approved indication for AMD therapy, it is the least costly option for treatment. Between 2008 and 2015, the use of bevacizumab over other agents is estimated to have saved Medicare at least $17.3 billion, corresponding to a $13.8 billion savings to Medicare and a $3.5 billion savings to patients.[31]

When evaluating treatment options, decision makers need to take real-world evidence into consideration. In a retrospective analysis of MarketScan Research Databases, the frequency and cost of ranibizumab and aflibercept injections were generally comparable in neovascular AMD. In treatment-naïve patients with neovascular AMD, per-patient injection frequency and cost were not significantly different between those who received ranibizumab versus aflibercept over 12 months (5.62 vs 5.54; $P = .52$, and $11,351 vs $10,702; $P = .06$, respectively) and 24 months (7.86 vs 8.37; $P = .16$, and $16,286 vs $16,666; $P = .69$, respectively).[32] In previously treated patients with neovascular AMD, there was no significant difference in injection frequency (5.95 vs 6.09, $P = .56$) or treatment cost between ranibizumab and aflibercept over 12 months. At 24 months, injection frequency was significantly lower among ranibizumab- versus aflibercept-treated patients (7.98 vs 9.63; $P = .03$); however, treatment costs were comparable ($16,303 vs $19,361; $P = .13$).[32]

In a retrospective database analysis of 49,485 eyes, researchers found that patients with neovascular AMD receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients receiving fixed, frequent therapy in randomized controlled trials.[33] This study demonstrates the gap between administration in practice compared with administration in a controlled trial setting. Although patients in clinical trials receive fixed, frequent therapy, in real-world practice, patients will have less than ideal adherence. This highlights the need for a clinically effective regimen with a lower injection burden.

Horner et al reported the long-term effectiveness of a PRN ranibizumab protocol in patients with neovacular AMD. Researchers examined 95 eyes from 86 patients who completed 8 years of follow-up in a single treatment center. At year 8, 47.4% had stable or improved vision; 10.5% gained greater than or equal to 15 letters; and 33.7% lost 15 or more letters. The median injection frequency was 6 in year 1 and 3 injections in year 8. The mean number of total injections per eye over 8 years was 31.6.[34]

Future Therapy: Biosimilar Options

The situation is further complicated by the fact that biosimilars for bevacizumab are in continual development, with the first one approved for use in July 2019; however, the degree to which these will be repackaged for intravitreal administration by compounding facilities has yet to be elucidated.[35,36] In addition, biosimilar versions of aflibercept and ranibizumab are also undergoing study.[35] The actual effect of the entrance into the market of biosimilar options for treatment of neovascular AMD remains unclear at this time. However, because Medicare shoulders the burden of paying for neovascular AMD care, managed care professionals and payers should pay close attention to Medicare policies affecting biologics and biosimilar reimbursement. Medicare payment for biologics is based on the agent's average sales price, net rebates, and other discounts, plus a fixed percentage. A smaller mark-up can penalize prescribers who pick a lower-cost drug. To remedy the disincentive to prescribe a lower-cost biosimilar, Medicare biosimilars payment includes a fixed percentage based on the reference biologic. Medicare has also implemented a new biosimilar payment policy that pays a blended average sales price for all biosimilars of a reference biologic drug, plus the fixed percentage of the reference biologic.[37]

Managed Care Issues and Strategies to Optimize Patient Outcomes

Collaboration With Retina Specialists and the Importance of Formulary Options

Retina specialists are seeing increasing numbers of patients with neovascular AMD, and specialty practice is complicated by the fact that they place a high value on having access to all available anti-VEGF treatment options in order to individualize care for all

patients, especially those considered difficult to treat. Because of this, a comprehensive anti-VEGF agent inventory in ophthalmology practices is a critical consideration along with drug efficacy and cost-effectiveness. The proportion of practice time devoted to patients with AMD is also an important factor in patient management. A time-motion study estimated that caring for patients with AMD consumes 20% of ophthalmology practice office time. An office visit for an intravitreal injection can take anywhere from 1.5 to 4 hours. Patient burden surrounding therapy must also be considered. Patients have reported that the average therapy visit can encompass as much as 12 hours, from preparing to leave home to individual postinjection recovery, which can take as long as 9 hours.[3,15] Managed care providers and payers must keep these additional factors in mind and optimize communication with retina specialists to provide the most clinically effective and cost-effective treatment strategies, along with safe and efficient drug administration and patient care.

The dilemma that managed care organizations face with respect to the anti-VEGF agents is cost. Managed care organizations are charged with walking the fine line of controlling cost while providing access to quality healthcare services. Relatively speaking, the cost of the FDA-approved anti-VEGF agents can be much costlier than the off-label anti-VEGF agents that many retina specialists consider as first-line therapy in neovascular AMD.

The difficulties associated with this situation are many. Typically, managed care organizations do not provide coverage for off-label indications, unless the off-label use is documented in the medical compendia to be adopted as a standard of care. As a specialty, retina specialists have not endorsed the use of the off-label anti-VEGF agent. The regimens being utilized today by retina specialists are in a constant flux ranging anywhere from changes in treatment duration, treatment frequency, or even the new concept of treat and extend. Changes in the treatment regimen will change the cost of the regimen. As the regimen is modified, cost-effectiveness evaluations will also change.

Finally, with respect to clinical outcomes, based on the clinical trials, anti-VEGF treatments may be viewed as similar. Evaluation of a clinical outcome is difficult due to the lack of any standardized accepted metric to measure outcomes and benefit. Any differences in clinical outcomes due to differences in the patient populations or differences in the treatment regimen, by whatever means to measure, will most likely need to be evaluated further in real-world data and experience.

The treatment of neovascular AMD is likely not a high priority for managed care organizations today, given the higher cost of medications in other specialty areas. As such, managed care organizations are not familiar with subtle intricacies or clinical justification that would drive a specific anti-VEGF selection. Managed care organizations will use treatment guidelines, recommendations, or consensus that will help define the treatment options and process, as well as utilize key opinion leaders in their networks to help define the treatment selection process. It is incumbent upon the retina specialists to work with their managed care organizations to educate them on specific intricacies in the treatment selection process, as well as on any differences in clinical outcomes resulting from these intricacies, using real-world data and evidence. Such open dialogue between specialists and payers will lead to a greater appreciation of management expectations, as well as to minimization of barriers to the prior authorization/precertification criteria.

The Role of Specialty Pharmacies

The specialty drug market continues to grow at double-digit rates, and the specialty pharmacy provider market is also growing in tandem. Specialty pharmacies play a critical role in the provision of anti-VEGF therapies, including repackaging products for single use. These specialists are also keenly aware of potential adverse effects associated with individual therapies and can assist in patient surveillance and monitoring. In a recent Kantar Health Payer Survey, the proportion of payers encouraging the use of specialty pharmacies to manage physician-administered injectable agents grew from 29% in 2014 to 36% in 2016. A total of 24% of payers mandated the use of specialty pharmacies for certain drugs during this period. In addition, 36% of payers encouraged the purchase of physician-administered intravenous drugs through specialty pharmacies via the development of more favorable reimbursement policies for these therapies.[15,38]

As new products for treatment of neovascular AMD with different mechanisms of action are being developed and marketed, clinicians are likely to use both new options and potential combination therapy to obtain better efficacy and longer-lasting results. Therapy selection and costs will evolve over time with an increase in the use of emerging agents and multiple products. Switching between products after less-than-optimal results will likely become more common.[39] There remains a need to consolidate and define parameters for switching opportunities, and further insight into the mechanisms of anti-VEGF resistance is also needed to guide treatment decisions on when and how to switch.[40] Managed care professionals and payers, retina specialists, and specialty pharmacists must collaborate to evaluate pipeline agents and new regimens, and to select the best treatment options for individual patients.

Conclusions

Neovascular AMD is a severe ophthalmic disease than can seriously and negatively impact an affected patient's health and functioning with progressive vision loss and even eventual blindness. The development and emergence of anti-VEGF therapies for neovascular AMD has significantly altered the treatment and patient management landscape, bringing great benefit by preserving vision in those with the disease. However, both the disease burden and the costs of its therapies can have a substantial financial impact on patients. The

costs of healthcare are further complicated by the fact that most patients with neovascular AMD are covered by Medicare and thus affected by the accompanying regulations and restrictions placed on their therapy. The quest to determine the most cost-effective and valuable treatment strategies for neovascular AMD continues to be an important focus of patient management. Collaborating together, managed care professionals, retina specialists, and specialty pharmacists all play key roles in working with patients with neovascular AMD, including addressing the costs associated with the disease and its treatment. With their input and collaboration, therapy and overall management of patients with AMD can be optimized to reduce disease progression and improve overall outcomes. ■

Author affiliation: Winston Wong, PharmD, is president of the W-Squared Group, Longboat Key, FL.

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Address correspondence to: wwong@wsquaredgroup.com.

Medical writing and editorial support: Elizabeth Paczolt, MD, FACNM.

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POSTTEST

Improving Treatment Strategies for Wet Age-Related Macular Degeneration

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which statement about the burden of age-related macular degeneration (AMD) is most accurate?

A. Although blindness attributed to AMD has declined, the number of patients with AMD is increasing.
B. The numbers of patients with AMD and blindness attributed to AMD are both increasing.
C. The number of patients with AMD is declining, but blindness attributed to AMD is increasing.
D. The numbers of patients with AMD and blindness attributed to AMD are both decreasing.

2. Which investigational regimen binds both vascular endothelial growth factor (VEGF)-A and Ang-2?

A. Bevacizumab
B. Brolucizumab
C. Faricimab
D. Aflibercept

3. Which investigational drug that is being evaluated to treat neovascular AMD is an intravitreal formulation of bevacizumab?

A. FYB201
B. ONS-5010
C. ADVM-022
D. RGX-314

4. What is the maximum dosing interval for the treat-and-extend injection regimen?

A. 2 weeks
B. 12 to 16 weeks
C. 24 weeks
D. 52 weeks

5. RM is a 76-year-old man with neovascular AMD, coronary artery disease, and chronic obstructive pulmonary disease. He has been receiving monthly intravitreal bevacizumab injections for more than 2 years. His visual acuity is stable, and the macula appears dry on optical coherence tomography monitoring. RM recently lost a reliable source of transportation to clinic appointments. He would like to know if he could schedule clinic visits less frequently. Which anti-VEGF agent on-label is approved for dosing every 8 to 12 weeks after 3 monthly loading doses?

A. Aflibercept PRN regimen
B. Ranibizumab PRN regimen
C. Brolucizumab
D. There are no anti-VEGF agents approved for dosing every 8 to 12 weeks.

6. Which investigational anti-VEGF agent for the treatment of neovascular AMD has the potential to provide 6 months of continuous intravitreal exposure?

A. Abicipar pegol
B. Faricimab
C. Conbercept
D. Ranibizumab port delivery system

7. Which percentage represents the approximate decline in quality of life (QOL) in patients with AMD and very severe vision loss?

A. 40%
B. 50%
C. 60%
D. 70%

8. **What is one of the key vision-related functions patients with neovascular AMD want to retain to maintain their QOL?**
   A. Ability to walk
   B. Facial recognition
   C. Hand-eye coordination
   D. Unrestricted eye movement

9. **Per data from Polat et al, approximately what percentage of patients have been found to be noncompliant with their anti-VEGF therapy regimen for neovascular AMD?**
   A. 10%
   B. 20%
   C. 30%
   D. 40%

10. **What was the approximate cost associated with the 2.5 million intravitreal anti-VEGF injections paid for under Medicare in the year 2013?**
    A. $100 million
    B. $200 million
    C. $300 million
    D. $400 million

NOTES

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