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A Managed Care Review: Approaches to Mitigate Blindness Associated with Neovascular Age-Related Macular Degeneration

HIGHLIGHTS

› Review of Neovascular Age-Related Macular Degeneration Treatment Options

› Managed Care Opportunities for Treatment for Sight Preservation

› CE Sample Posttest

Supplement to *The American Journal of Managed Care®*

Approaches to Mitigate Blindness Associated with Neovascular Age-Related Macular Degeneration

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Intended Audience

Pharmacists and managed care professionals

Activity Overview

Age-related macular degeneration (AMD), which affects approximately 8 million Americans, has dramatically changed with the introduction of biologic therapies. Two approved and 1 off-label anti-vascular endothelial growth factor (VEGF) biologics are now used effectively and safely to prevent vision loss and blindness. Healthcare costs associated with drug therapy, hospitalization, and reduced productivity for AMD-related care are significant; indirect costs are high and grow as vision loss progresses. Early, aggressive treatment can help control costs later in life. This activity will help managed care professionals become more aware of the prevalence of AMD, economic implications of various treatment plans, and opportunities to optimize the care of patients through counseling and therapy monitoring.

Statement of Educational Need

As the population ages, certain age-related diseases are proliferating both in the United States and globally. Depending on the disease, available treatments, costs, and quality of life impact, some diseases are easier to mitigate. With recent developments in the treatment of neovascular age-related macular degeneration (nAMD), this disease is one that can be attacked directly with available therapeutic options, if detected early enough and treated aggressively enough. The burden of blindness has high personal and societal impact as measured by researchers and experienced by individuals who live through the devastation that blindness can impose on the life of patients and those who care for them. There is a need among the managed care audience to understand the clinical efficacy, safety, and handling properties of the treatment options that are emerging and available for the treatment of AMD. Payers and managed care pharmacists need to be experts in the use of advanced biologics in the treatment of AMD to have a significant impact on outcomes for a growing portion of the aging population.

Educational Objectives

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

- Examine the prevalence, pathophysiology, and risk factors of neovascular age-related macular degeneration (nAMD).
- Examine routes of administration, dosing, safety, clinical efficacy, and clinical role in treatment for FDA-approved and emerging anti-VEGF treatments.
- Examine the healthcare utilization costs associated with blindness and AMD.
- Apply knowledge of economics, treatment options, and clinical data to develop cost management strategies for AMD.

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Approaches to Mitigate Blindness Associated with Neovascular Age-Related Macular Degeneration

OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of therapeutic management of age-related macular degeneration, including the potential cost implications.

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Review of Neovascular Age-Related Macular Degeneration Treatment Options

Nancy M. Holekamp, MD

ABSTRACT

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

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For author information and disclosures, see end of text.

Disease Overview

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

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

Staging and Pathophysiology of AMD

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

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

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

Epidemiology of AMD

The risk of late AMD, including nAMD and geographic atrophy, increases exponentially in advanced age.[1,2,11] The Beaver Dam Eye Study examined the incidence of disease in a cohort of patients aged 43 to 86 years.[11] The 15-year cumulative incidence in the entire cohort was 14.3% for early AMD and 3.1% for late AMD. For those aged 75 years or older, the cumulative incidence was 24% for early and 8% for late AMD.[11] A meta-analysis of studies that used fundus photography and standardized protocols to assess disease prevalence found a progressive increase in the incidence of both early and late AMD with age.[2] Prevalence increased rapidly after age 75 years, especially in those of European descent. The overall prevalence of late AMD across all ethnicities was 0.15% for those aged 50 to 59 years, 0.47% for those aged 60 to 69 years, 1.46% for those aged 70 to 79 years, and 3.21% for those aged 80 to 84 years.[2]

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

Due to an aging population and increasing life expectancy, the number of Americans with late AMD, including nAMD and geographic atrophy, is increasing.[1] The number of cases rose from 1.75 million in 2000 to 2.07 million in 2010, an increase of 18%, and is expected to increase to almost 3.7 million in 2030 and 5.4 million in 2050. Although white individuals will continue to account for the majority of patients, cases of AMD in Hispanic Americans are expected to increase almost 6-fold by 2050.[1] Whereas the incidence of late AMD is increasing, a study that examined the 5-year risk of disease across generations in the 20th century suggests that the incidence of early or intermediate AMD has declined by 60% with each successive generation.[12] This suggests that modifications in environment, behavior, or lifestyle may reduce the risk of AMD.

Risk Factors for Progression to Late AMD

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

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

Diagnosis and Monitoring of Neovascular AMD

A comprehensive dilated eye examination is often necessary to diagnose early or intermediate AMD because it is usually asymptomatic.[9]

TABLE 1. Dry versus Wet AMD[9]

Dry (geographic atrophy)	Wet (neovascular AMD)
• About 90% of AMD cases	• About 10% of AMD cases
• Can become "wet"	• Accounts for 90% of central visual acuity loss
• Drusen form on the macula	• Neovascularization of the macula
• No angiogenesis	• Angiogenesis driven by VEGF
• No current treatment	• Treated with intravitreal anti-VEGF agents

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

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

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

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

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

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

Prevention of AMD

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

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

Current Treatment Options and Management Approaches

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

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

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

Anti-VEGF Agent Safety

Ocular severe AEs of intravitreal anti-VEGF therapy include rare reports of infectious and noninfectious endophthalmitis, retinal detachment, and increased intraocular pressure.[9,34] Whereas systemic AEs have periodically been raised as a concern, a large body of evidence indicates that the risk of systemic AEs with intravitreal injections of anti-VEGF agents remains below the level of detection.[43,44] A 2014 Cochrane review did not find a difference in the risk of serious systemic AEs between intravitreal ranibizumab and bevacizumab.[45] Results of a 2019 Cochrane review that evaluated aflibercept, bevacizumab, and ranibizumab found no difference in serious systemic AEs between anti-VEGF agents or control groups.[46]

Formulation Issues in Product Selection

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

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

TABLE 2. Properties of Anti-VEGF Agents[33,38-42]

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

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

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

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

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

Medical Society Recommendations for Anti-VEGF Agents in Neovascular AMD

Clinical practice guidelines from the United States and Europe commonly agree that 2 years of treatment with an available intravitreal anti-VEGF agent is safe and effective.[7,9,20,34,35] Bevacizumab and ranibizumab had comparable efficacy in the Comparison of AMD Treatment Trial (CATT), the Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) trial, and the Groupe d'Etude Français Avastin versus Lucentis dans la DMLA néovasculaire (GEFAL) study. Aflibercept and ranibizumab had comparable efficacy in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1, VIEW 2) trials.[34] A caveat is that bevacizumab and aflibercept have not been compared head-to-head.[7] In the 2018 ASRS survey, the first-line agent of US retinal specialists for nAMD was bevacizumab (70.2%), followed by aflibercept (16.4%), and ranibizumab (12.8%).[57]

Dosing and Monitoring of Anti-VEGF Agents

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

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

As-Needed versus Treat-and-Extend Approach

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

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

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

Individualization of Anti-VEGF Therapy

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

Anti-VEGF agents have specific attributes that may benefit individual patients based on their priorities and goals for treatment. For example, bevacizumab is an option for patients with end-stage AMD with poor visual acuity and whose highest priority is avoiding out-of-pocket expenses. An analysis based on data from the CATT found it more cost-effective compared with ranibizumab in newly diagnosed patients aged 80 years or older.[63] On the basis of potentially greater safety, ranibizumab may be the preferred agent for patients who are aged 85 years or older. Results from a European Medicines Agency Public Assessment report for aflibercept demonstrated a potentially higher rate of cerebrovascular events with aflibercept compared with ranibizumab in patients aged 85 years or older.[64] In a meta-analysis of ranibizumab AEs in this age group, there were no reports of an increase in the risk of total nonocular serious AEs, arterial thromboembolic events, cardiovascular events, or Antiplatelet Trialists' Collaboration events compared with controls. There were too few cerebrovascular events or deaths to evaluate these end points.[65]

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

Emerging Treatment Options for Age-Related Macular Degeneration

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

Abicipar Pegol

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

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

Brolucizumab

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

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

Brolucizumab was noninferior to aflibercept in the primary outcomes in both studies.[74] More than half of patients receiving brolucizumab 6 mg continued on the 12-week dosing interval through week 48, a reduction of 2 injections per year. In the prespecified superiority analysis of HAWK at week 16, the incidence of disease activity was lower with brolucizumab 6 mg compared with aflibercept (24.0% vs 34.5%; $P = .001$). Superiority was also demonstrated for CST reduction and presence of IRF/SRF.[74]

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

Faricimab

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

ONS-5010

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

Ranibizumab Port Delivery System

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

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

Intravitreal Anti-VEGF Biosimilars

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

Management of Neovascular AMD in Managed Care

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

Conclusions

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

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Managed Care Opportunities and Approaches to Supporting Appropriate Selection of Treatment for Sight Preservation

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ABSTRACT

When evaluating the impact of vision-destroying diseases, pharmacologic therapies represent a significant cost to patients, insurance providers, and society. Currently, up to 11 million people in the United States have some form of age-related macular degeneration (AMD), which is one of the leading causes of vision loss in older Americans. Ophthalmologists have administered more than 6 million intravitreal injections of aflibercept, bevacizumab, pegaptanib, and ranibizumab last year. Comprehensive assessment requires managed care administrators and clinicians to understand the direct and indirect costs of vision loss as well as the comparative safety and efficacy profiles for each agent. In AMD, it is critical to understand the established and emerging treatment patterns.

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For author information and disclosures, see end of text.

Introduction

Visual impairment has a significant impact on many aspects of a patient's life. Although many individuals with vision impairment live independently, caregivers and society typically assume the burden of caring for these patients. When evaluating the impact of diseases that affect vision, pharmacologic therapies represent a significant cost. Yet clinicians, policy makers, and managed care administrators must also consider the total disease burden, including indirect costs. This is particularly important as the number and kind of therapies for age-related macular degeneration (AMD) increase.

AMD leads to a loss of the sharp, fine-detail "straight ahead" vision required for activities such as reading, driving, recognizing faces, and seeing the world in color. As the disease progresses, patients lose more of their vision field. AMD is a leading cause of legal blindness and visual impairment in the United States and around the world.[1,2] The risk of developing advanced AMD increases from 2% for people between 50 and 59 years of age to almost 30% in people older than 75 years. Currently, as many as 11 million people in the United States have some form of AMD, and it is the leading cause of vision loss in Americans aged 60 years and older. This number is expected to double to nearly 22 million by 2050.[3,4] Currently, just 10% of patients experience neovascular (wet) AMD (nAMD) for which existing treatments are indicated.

Aflibercept, bevacizumab, pegaptanib (which has been largely replaced by the other agents because of their better efficacy),[5] and ranibizumab have changed how AMD is treated. These treatments have only been approved for the treatment of nAMD. An indication of how quickly anti-vascular endothelial growth factor (VEGF) utilization has grown is underscored by Medicare payments for physician services associated with the administration of anti-angiogenic drugs. In 2000, physicians reported 3000 Medicare-covered intravitreal injections. In 2008, they reported 1 million, and, in 2013, Medicare paid for 2.5 million intravitreal injections at a cost of more than $300 million.[6] The American Academy of Ophthalmology (AAO) estimated that more than 4 million intravitreal injections were administered in 2014, and experts estimate more than 6 million were given in 2016.[7]

The Ultimate Cost: Visual Impairment

Visual impairment affects individuals, caregivers, and society as a whole in a ripple effect. In a comparison of community-dwelling, older Americans with and without vision impairment, visually impaired individuals reported significantly more disability, even with simple daily activities, than those with acceptable vision. Vision loss can lead to loss of independence.

For example, people who reported vision problems were significantly more likely than others to report difficulty getting into or out of a chair or bed, accessing outside places, preparing meals, shopping for groceries, handling money, and managing medication. Visually impaired individuals also reported a negative impact when participating in activities such as meetings, talking on the phone with friends and relatives, and partaking in various social activities. Among patients who are older than 70 years, those with vision problems were twice as likely to report depression, recent falls, or a broken hip.[8]

The economic consequences of vision impairment are significant. A review of 22 interventional, noninterventional, and cost-of-illness studies quantified the direct costs, indirect costs, and intangible effects related to visual impairment and legal blindness.[9] Hospitalization, use of medical services related to the visual impairment diagnosis, and treatment all contributed the most to direct medical costs. Assistive devices and aids, home modifications, and healthcare services, such as home-based nursing or nursing home placements, were the major contributors to direct nonmedical costs. As visual impairment worsened, costs for support services and assistive devices increased; these were coded as direct nonmedical. Time spent caring for or assisting visually impaired individuals correlated to the degree of visual impairment, with individuals with most severe visual impairment requiring the most assistance. The time spent by caregivers 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 an individual with a visual acuity of 20/250 or worse.[9]

Indirect costs that were associated with visual impairment are also significant. These costs, which emanate from patient and caregiver impact, include productivity losses, employment changes, income loss, premature mortality, and dead-weight losses (the costs to society created by market inefficiency).[9]

Economic Implications of Age-Related Macular Degeneration

A number of studies have attempted to quantify the economic costs associated with visual impairment, but few separate the burden by underlying diagnosis. Most authors still rely on figures calculated by Rein et al in 2006. They estimated the total economic burden of major visual disorders in 2004 dollars at $35.4 billion, which included $16.2 billion in direct medical costs, $11.1 billion in indirect costs, and $8 billion in lost productivity. Annually, the federal government and state Medicaid agencies are responsible for at least $13.7 billion of these costs.[10] These figures are 12 years old, but no recent studies with updated data have been located.

A cross-sectional, prevalence-based healthcare economic survey assessed the annual, incremental, and societal costs associated with nAMD. They included direct ophthalmic medical costs, direct nonophthalmic medical costs, direct nonmedical costs, and indirect medical costs that are associated with nAMD in 4 cohorts. Patients with nAMD (n = 200, designated "the study cohort") were compared with a control cohort of patients with good (20/20–20/25) vision. Three other cohorts included patients with diminishing vision in their better-seeing eye. Patients in the control cohort incurred a mean of $6116 in expenses, whereas those with AMD incurred an average of $39,910. Individuals whose impairment had no light perception incurred $82,984. Direct ophthalmic medical costs decreased, and indirect costs also decreased as a percentage of the total societal costs as patients' vision worsened. In the study cohort, direct costs represented 17.9% of the overall total. Among the controls, direct costs were 74.1% of total societal costs. In individuals with no light perception, direct costs were 10.4% of total societal cost, indicating considerable indirect costs.[11]

Age-Related Macular Degeneration Treatment Costs

Based on safety and efficacy evidence, clinicians currently use intravitreal bevacizumab, aflibercept, and ranibizumab injection.[12] Although researchers have published several cost-effectiveness studies about nAMD therapies, many included older treatments, such as laser photocoagulation, photodynamic therapy, and the early anti-VEGF medication pegaptanib.[13] The direct cost of nAMD treatment in 2004 dollars was estimated at $575 million, which is expected to increase as society ages and more costly treatments are introduced.[3,10]

Ophthalmologists and policy makers want to know specifics when they consider the costs of AMD. Safety and efficacy are always primary concerns, and sufficient data are available to confirm that these agents are safe and approximately equally effective.[12] The primary treatment goal of AMD is to restore or maintain vision, which is critical to the patient's overall quality of life (QOL). The anti-VEGF agents improve vision-related quality of life (VRQOL) for patients with nAMD. Patients whose vision is maintained have better VRQOL, irrespective of which eye is treated (better or worse seeing eye).[14]

Stakeholders regularly compare new options to old options; those studies generally precede head-to-head comparisons. As early as 2011, researchers working in pharmacoeconomics compared laser photocoagulation and photodynamic therapy with verteporfin and intravitreal bevacizumab, pegaptanib, and ranibizumab. Anti-VEGF therapies appeared to be highly cost-effective compared with old therapies. The researchers indicated that although the anti-VEGF treatments improved visual acuity compared with older therapies,

their increased cost was troublesome. Researchers concluded that ranibizumab was consistently shown to be a cost-effective therapy for nAMD compared with all other approved options. The cost-effectiveness of pegaptanib was marginal, depending on the disease stage. Few published studies compared active treatments at that time, and the researchers did not find any acceptable studies that addressed the off-label use of bevacizumab.[13]

Next, clinicians wanted long-term data about cost-effectiveness for options; patients who have nAMD can live with the disease for 20 years or longer.[5] US data for bevacizumab became available in 2012 when researchers with the Veterans Affairs San Diego Healthcare System and University of California San Diego analyzed the cost-effectiveness of monthly ranibizumab and bevacizumab.[15] The researchers developed a Markov model with 3-month cycles in a hypothetical cohort of 65-year-old patients (N = 1000) with nAMD. The economic analysis included physician visits, drugs, and monitoring costs. The total direct cost for bevacizumab was $30,349 per patient with a mean average of 21.6 quality-adjusted life-years (QALYs) over 20 years compared with $220,649 for ranibizumab with a mean average of 18.1 QALYs. Compared with ranibizumab, treatment with bevacizumab resulted in an incremental cost-effectiveness ratio (ICER) of −$54,649 to gain 1 additional QALY. Based on a willingness-to-pay (WTP) of $50,000, the researchers predicted bevacizumab would be more cost-effective than ranibizumab 95% of the time.[15] These findings were replicated in 2013.[16]

Confirmation studies are of interest, especially when new dosing strategies are being explored. A 2014 cost-effectiveness analysis examined a hypothetical cohort of 80-year-old patients with newly diagnosed neovascular macular degeneration.[17] The study looked at monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, or as-needed ranibizumab over a period of 20 years. In addition to costs, the researchers examined the potential for differences in risks of serious adverse effects (AEs) and therapeutic effectiveness. They concluded that[17]:

- ICERs for monthly bevacizumab and monthly ranibizumab for nAMD were $242,357/QALY and $10,708,377/QALY, respectively.
- As-needed ranibizumab was more costly and less effective than bevacizumab, and bevacizumab along with as-needed dosing represented the best value.
- When the researchers varied the model parameters (ie, the proportion of patients with serious systemic AEs, the number of injections administered, the cost per injection, and patient's life expectancy), bevacizumab was preferred in nearly two-thirds of the simulations using WTP of $100,000/QALY.

Medicare: Bearing a Disproportionate Share

As Medicare bears most of the cost of AMD, studies about the spending are important. A 2011 retrospective, longitudinal cohort study compared random sample cohorts from 1994, 2000, and 2006. The length of the study is important as several new treatments became available during that time. Between 1994 and 2006, the number of beneficiaries who were newly diagnosed with nAMD increased by a factor of 2.41. Annual part B payments increased significantly from $3567 in 1994 to $5991 in 2006 per beneficiary and were adjusted to 2008 dollars. Payments for eye care alone roughly doubled from $1504 in 1994 to $3263 in 2006, with anti-VEGF injections accounting for 73% of the cost. Payments for laser photocoagulation decreased significantly. The researchers noted that they observed a shift from pegaptanib and ranibizumab to bevacizumab between 2006 and 2008; they predicted it would continue and would be associated with savings of about 80%.[18]

The trend toward bevacizumab developed as it was predicted. Researchers found significant geographic and demographic variations in treatment for AMD in Medicare beneficiaries in ensuing years. By 2009, just 35% of beneficiaries received ranibizumab for initial nAMD treatment, and black individuals were 45% less likely to receive ranibizumab than others. The geographic variation was large. Clinicians in urban areas, zip codes with high median incomes, and the New England and East South Central census regions were more likely to use ranibizumab.[19] From 2008 to 2015, statisticians estimated that using bevacizumab for AMD instead of ranibizumab or aflibercept saved Medicare a conservative $17.3 billion because beneficiaries enrolled in Medicare Advantage plans were excluded from the study.[20]

Keeping an Eye on Off-label Concerns

Researchers note that dollar-for-dollar, bevacizumab is significantly less expensive than the FDA-approved anti-VEGF inhibitors, but a compounding pharmacy must prepare it. Some safety concerns about endophthalmitis surfaced in 2011, and others have been identified (see **Table 1**).[5,21-27] Regulatory bodies have implemented additional oversight since identifying outbreaks of endophthalmitis. Compounding pharmacies are required to comply with United States Pharmacopeia Chapter <797>, which sets standards for compounding, transporting, and storing compounded sterile product. Clinicians should ensure that they use reliable sources of bevacizumab. The AAO guidelines recommend that clinicians include discussion of the risks and benefits of treatment and treatment alternatives, including the off-label status of bevacizumab for AMD when they consider using this monoclonal antibody.[28] On the other hand, clinicians should also note that a 2015 study did not find an increased risk of endophthalmitis compared with ranibizumab.[27] Stability studies have found that bevacizumab repackaged in plastic syringes is stable for 3 to 6 months, if handled properly.[29,30]

Following the publication of studies that demonstrate the clinical equivalence of ranibizumab and bevacizumab for nAMD,

the majority of the cost analyses have been performed on these agents. Although the 2010 Patient Protection and Affordable Care Act prohibits the use of QALYs for making reimbursement decisions in the United States, QALYs are used frequently outside of the country.[31,32] Using QALYs, a 2007 British study found that bevacizumab would need to be approximately 40% as effective as ranibizumab for the treatment of classic AMD for ranibizumab to achieve £30,000 ($39,106 in 2019 US dollars) per QALY, which is the threshold for drug approval of the National Institute for Health and Care Excellence.[33] In the United Kingdom, it wasn't until 2018 that bevacizumab was approved for use in nAMD.[34]

In a 2009 review of 44 cost-effectiveness studies in AMD, the researchers determined that older treatments, such as laser photocoagulation and photodynamic therapy, were cost-effective compared with no treatment. New therapies, such as ranibizumab, were more cost-effective than older treatments. Across the studies analyzed, at least 5 years of treatment was necessary to show cost-effectiveness for the new and clinically effective treatments for nAMD at standard WTP thresholds compared with older, less-effective therapies such as laser photocoagulation.[13]

The 2011 FDA approval of aflibercept for nAMD introduced another option. Aflibercept's phase 3 clinical trial results suggest that this agent might have a longer duration of action than ranibizumab or bevacizumab. With the approval of aflibercept, managed care administrators and clinicians looked for comparative data. European researchers created a model that compared ranibizumab (as needed), aflibercept (bimonthly), and bevacizumab (as needed). In Europe, bevacizumab treatment costs €27,087 ($31,677 in 2018 US dollars) per year, about €4,000 ($4678) less than aflibercept and €6000 ($7016) less than ranibizumab. Based on an assumption of similar effectiveness for all drugs, these researchers also found that bevacizumab was the most cost-effective.[35]

Managed Care Strategies to Optimize Outcomes

Managed care organizations need to consider the financial implications of physician-administered drugs in 2 ways: a microeconomic (patient and ophthalmologist) perspective and a macroeconomic (societal) perspective. At the microeconomic level, managed care organizations should be aware that professional associations provide limited guidance on cost considerations when selecting ophthalmic anti-VEGF agents.[36]

As most patients with AMD are Medicare beneficiaries; part B covers 80% of physician-administered drugs, and patients cover the remaining 20% of the allowable reimbursement for the drug and the associated physician administration charges. The differential is $400 to $500 for aflibercept and ranibizumab compared with approximately $11 for bevacizumab.[7,37]

Out-of-pocket (OOP) costs can accumulate rapidly for patients, so managed care organizations should understand their patient demographics. Managed care organizations also need to consider a patient's indirect costs.[37] Policy makers need to be aware that in terms of time required to complete office visits, treating AMD is burdensome for patients and the ophthalmology staff. Office staff reports that patients with AMD consume 20% of their time. An average patient visit for nAMD is 90 minutes, but it can sometimes be as long as 4 hours. Patients report that the average visit takes about 12 hours from preparing to leave the home to post-appointment recovery, which can take up to 9 hours.[38]

Anti-VEGF drug costs for ophthalmologists can also be daunting, so managed care plans need to know how drug procurement is structured for practitioners. Ophthalmologists prefer to have biologics on hand because they do not know whether patients will need treatment until they examine the affected eyes.[7] Patients who will have to pay for and maintain their own drug inventories may find it risky. A policy for determining how to deal with patients who cannot afford the 20% copayment is also a necessity, as ophthalmologists cannot be expected to absorb costs of $400 to $500 per treatment.[37]

Managed care organizations can address the costs associated with biologics for AMD in several ways. They may consider implementing or refusing to implement a white bagging process, a requirement that replaces buy-and-bill with purchasing the agents through a specialty pharmacy. They can make a case for payers to be compensated fairly for overhead costs that are typically 25% to 30% of average wholesale price. Large systems may find that developing their own specialty pharmacy or collaborating with other organizations may be cost-effective.[7,39]

Managed care organizations also need to be cognizant of early diagnosis and treatments that are essential. AMD can progress and cause vision loss rapidly, so even minor delays in treatment can have tremendous impacts on vision. For some patients, monthly office-based assessments will be insufficient.[40] Implementing better screening programs, increasing public awareness, and treating aggressively are essential. Other factors can influence how patients

TABLE 1. Facts About Compounded Intravitreal Bevacizumab[5,21-27]

- Compounding pharmacies must repackage bevacizumab into single-dose, prefilled syringes for intravitreal use.
- Some ophthalmologists have reported the presence of large silicone oil droplets that are often symptomatic and suspected to be associated with the insulin syringe used for preparation.
- Outbreaks of endophthalmitis and noninfectious inflammatory response have been reported among patients with neovascular AMD who received bevacizumab injections that were repackaged by the same pharmacies.
- During repackaging, handling, and distribution, bevacizumab's protein concentration and potency can decrease.
- Counterfeit bevacizumab has been identified in the supply chain periodically.

AMD indicates age-related macular degeneration.

respond to treatment and need to be considered when selecting treatment (see **Table 2**[5]).

At a macroeconomic level, managed care plans should be forward-looking and estimate how they expect the number of patients with AMD to grow. There are other issues to consider, including[6,37]:

- If the allowable reimbursement is less than the costs of the drug (a situation that occurs more often than is acceptable)
- If rebates or purchasing discounts are available
- State and local sale tax regulations on gross revenue or drug revenues
- The number of intravitreal injections expected to be administered

Acknowledging that anti-VEGF biologic use is also expanding in diagnoses other than AMD (eg, diabetic retinopathy-associated macular edema and macular edema associated with retinal venous occlusive disease) is also prudent. If bevacizumab is used, the managed care organization should ensure that their compounding pharmacy is reliable, responsive, and trustworthy.[6,37]

Specialty Pharmacy's Role

The specialty pharmacist's role starts with appreciating the value of an early diagnosis and treatment. The National Health and Nutrition Examination Survey (NHANES) found that 84% of people with AMD were unaware of their condition.[41] During contact with aging patients, specialty pharmacists can encourage eye examinations and educate patients about eye health. Patients can access exceptional information about AMD from the AAO and the American Society of Retina Specialists.[42,43]

Prevention and lifestyle modifications are basic interventions, and pharmacists should be aware of appropriate approaches and recommendations. Eight million Americans aged 55 years and older are at high risk for developing advanced AMD. Age-related eye disease study supplementation could help roughly 300,000 at-risk individuals avoid advanced AMD and associated vision loss over a 5-year period.[42] Pharmacists must also promote educational campaigns and increase awareness about AMD risk factors including age, family history, cardiovascular risk factors, and cigarette smoking.[5]

Specialty pharmacists often provide anti-VEGF therapies and may have compounding roles in which they repackage products for single use. These tasks come with parallel responsibilities for monitoring potential systemic AEs and ensuring response and adherence.

Specialty pharmacists will continue to play a significant role in changing buy-and-bill models. A recent Kantar Health Payer Survey found that the percentage of payers encouraging the use of specialty pharmacies to manage physician-administered injectable agents (white bagging) grew from 29% in 2014 to 36% in 2016. The percentage of payers mandating the use of specialty pharmacies on certain drugs remained steady at 24% from 2014 to 2016. According to the study, 36% of payers encourage the purchase of physician-administered intravenous drugs through specialty pharmacies by creating favorable reimbursement policy (36% of payers).[44] This allows payers to purchase drugs and biologics at a better price, shift coverage from medical to pharmacy benefit, and increase visibility in their drug spending.[39]

In 2017, *The Lancet* published a study conducted by a multinational vision loss expert group that updated statistics on vision loss.[45] The report does not break down vision loss and legal blindness by cause, but it does deliver some good news. This group noted a reduction in the age-standardized prevalence of legal blindness and vision impairment in 2010, and the trend has continued. The authors cite research that indicates vision interventions. Intravitreal injections that have been available in the past 15 years provide some of the largest returns on investment.[46] Managed care organizations, clinical staff, and affected patients need to embrace that fact.

TABLE 2. Patient Factors That Influence Treatment Selection[5]

- Age
- General health and comorbidities
- Baseline visual acuity scores
- Anatomic characteristics
  - Location and extent of lesions
  - Presence of retinal fluid leakage
  - Hemorrhage
  - Fibrotic scarring
- Risks of AMD in the second eye
- Willingness and ability to adhere to treatment and monitoring regimens
- Initial treatment responses or resistance
- Threats to quality of life associated with vision loss

AMD indicates age-related macular degeneration.

Conclusions

Visual impairment and its associated costs affect not only patients but also caregivers, providers, and society. There are nonmedical costs to patients, such as the need for support services and assistive devices, and caregivers also incur substantial indirect costs that stem from lost productivity and income as a result of needing to assist patients with AMD with activities of daily living and attending appointments. To provide cost-effective treatments to patients with AMD, managed care professionals must consider that new treatment options are more cost-effective than older treatments. The surge in anti-VEGF utilization and Medicare-covered intravitreal injections has proven to enhance patients' VRQOL, but they are accompanied by high direct costs. In several economic and cost-effectiveness analyses, bevacizumab for the treatment of AMD was proved to be less costly and more effective compared with ranibizumab. Further complicating treatment decisions are the OOP costs for patients, which differ based on patient demographics and a lack of specific

guidelines. Despite the cost-effectiveness of bevacizumab, ranibizumab is more often preferred by clinicians in several geographic locations. Additionally, there are no existing policies that address challenges with elderly patients with AMD who are Medicare part B beneficiaries and cannot afford a 20% copayment after Medicare. As both the numbers of available treatment options for patients with AMD and the overall patient population continue to grow, managed care professionals must consider a multitude of factors that contribute to direct and indirect costs for these patients and society when initiating an appropriate, cost-effective therapy for a patient with AMD. ■

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POSTTEST

Approaches to Mitigate Blindness Associated with Neovascular Age-Related Macular Degeneration

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which of the following is a major modifiable risk factor for developing neovascular age-related macular degeneration (nAMD)?

A. Smoking
B. Complement factor H risk alleles
C. Sunlight exposure
D. Age-related maculopathy susceptibility (ARMS) 2 risk alleles

2. Which test is the primary tool for guiding decisions on the appropriate dosing interval in a treat-and-extend or as-needed approach to managing nAMD?

A. Preferential hyperacuity perimetry (PHP)
B. Optical coherence tomography (OCT)
C. Visual acuity
D. Fluorescein angiography

3. Which of the following statements about the role of nAMD (wet AMD) and geographic atrophy (dry AMD) is most accurate?

A. nAMD, which accounts for about 90% of AMD cases, is treated with anti-vascular endothelial growth factor (VEGF) agents.
B. Geographic atrophy, which accounts for about 90% of AMD cases, has no treatment options.
C. nAMD, which accounts for about 10% of AMD cases, has no treatment options.
D. Geographic atrophy, which accounts for about 10% of AMD cases, is treated with anti-VEGF agents.

4. Which of the following investigational drugs that is being evaluated to treat nAMD is a bispecific antibody that binds both VEGF-A and angiopoietin (Ang)-2?

A. Abicipar pegol
B. ONS-5010
C. Brolucizumab
D. Faricimab

5. Which of the following investigational drugs for the treatment of nAMD is being evaluated in a 12-week dosing interval during maintenance therapy?

A. Abicipar pegol and brolucizumab
B. Brolucizumab
C. Brolucizumab and faricimab
D. Abicipar pegol, brolucizumab, and faricimab

6. Shirley is a 67-year-old woman who awoke one morning with a small spot in her vision. She noticed that the blind spot tracked with her vision. She contacted her primary care physician who told her it was a floater. After 3 months, she saw an ophthalmologist. He gave her a diagnosis of nAMD. Which of the following statements is TRUE?

A. Shirley will probably maintain her independence for at least 20 years.
B. Adaptive devices and other indirect costs will be expensive at first, but less expensive over time.
C. Shirley should begin treatment with an anti-VEGF agent as soon as possible.
D. Shirley should consider pushing for laser photocoagulation before considering an anti-VEGF agent.

7. Which FDA-approved drug is indicated to be able to stretch treatments to every 12 weeks?

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

8. How has availability of effective intravitreal therapies affected the global trend with regard to loss of vision and blindness?

A. The age-standardized prevalence of blindness and vision impairment began falling before 2010, and the trend continues.
B. The age-standardized prevalence of blindness and vision impairment began rising before 2010, and the trend continues.
C. The age-standardized prevalence of blindness and vision impairment has been the same for 50 years.
D. No one has to take the lead to determine the age-standardized prevalence of blindness and vision impairment.

9. Which of the following would be a concern for managed care strategists at the macroeconomic level?

A. Ophthalmologist complaints about the cost of maintaining inventory
B. The hours patients spend scheduling, preparing for, and recovering from appointments
C. Patients' out-of-pocket costs
D. Allowable reimbursement, rebates, state and local tax regulations, and diagnoses projection

10. Among the following, which is the best plan for specialty pharmacists to address AMD thoroughly?

A. Educate patients, stress prevention strategy, counsel that AREDS supplementation is unnecessary until late in the disease process.
B. Educate patients, stress prevention strategy, counsel for early AREDS supplementation, monitor for adverse effects and response to anti-VEGF therapies.
C. Stress prevention strategy and smoking cessation, discourage AREDS use as it is costly and ineffective, promote early treatment with anti-VEGF therapies
D. Advocate for buy-and-bill models as the most reasonable option to procure anti-VEGF therapies.

NOTES

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