Innovative Approaches in the Treatment and Management of Retinal Diseases:

Managed Care Insights on the Evolving Role of Anti-VEGF Therapies

A CME/NCPD Approved Activity

JOURNAL of MANAGED CARE MEDICINE

This activity is supported by an educational grant from Regeneron Pharmaceuticals

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Learning Objectives:
1. Assess the clinical and economic burden of retinal diseases, including factors that contribute to poor prognosis and increased costs.
2. Evaluate treatment strategies and resources based on evidence for achieving the best patient outcomes in cases of retinal diseases.
3. Explain the mechanism of action, pharmacokinetics, efficacy, and dosing intervals of anti-vascular endothelial growth factor (VEGF) agents in the treatment of AMD and DME/DR.
4. Analyze current clinical guidelines and recommendations for the use of anti-VEGF therapies in AMD and DME/DR.
5. Describe how treatment innovations are improving durability, efficacy, and patient outcomes.
6. Assess medical benefit design approaches to streamline patient care to evidence-based treatments for retinal diseases.
7. Identify opportunities for managed care professionals to collaborate with other healthcare providers to improve access to care for patients with AMD and DME/DR, including addressing barriers to care such as cost, transportation, and lack of access to specialty providers.

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Dr. Graff has served as a consultant for Alimera, Hi-Health, IvericBio, Ocular Therapeutix, Regeneron, RegenxBio, and Roche/Genentech. He has received research/grant support from Kyowa Kirin, Ocular Therapeutix, Regeneron, Regenxbio, and Roche/Genentech.
Dr. Owens has served as a consultant for Baxter, Regeneron Pharmaceuticals and Sanofi.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, MS, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships with an ineligible company to disclose.

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Innovative Approaches in the Treatment and Management of Retinal Diseases: Managed Care Insights on the Evolving Role of Anti-VEGF Therapies

Post-Test Questions

1. Which form of age-related macular degeneration (AMD) more commonly causes vision loss?

   a. Neovascular AMD **b.** Non-neovascular AMD
   c. Macular edema AMD **d.** Non-central macular edema

2. In addition to age, which of the following is a risk factor for developing AMD?

   a. Hypertension **b.** Trauma to the eye
   c. Smoking **d.** Glaucoma

3. Which of the following is NOT a modifiable risk factor for developing diabetic retinopathy (DR)?

   a. Hyperglycemia **b.** Pregnancy
   c. Hyperlipidemia **d.** Obesity

4. Which of the following plays an important role in the development of pathology of AMD, diabetic macular edema (DME), and DR?

   a. Interferon alpha
   b. Tumor necrosis factor
   c. Angiogenesis factor ten
   d. Vascular endothelial growth factor (VEGF)

5. Which of the following agents is not currently FDA approved for treating nAMD, DR, or DME?

   a. Aflibercept **b.** Bevacizumab
   c. Ranibizumab **d.** Pegaptanib

6. Which of the following is a reason patients do not achieve optimal vision outcomes with anti-VEGF therapy?

   a. Patient nonadherence with treatment
   b. Overtreatment
   c. Lack of efficacy of anti-VEGF agents
   d. Lack of Medicare coverage

7. Which of the following regimens involves treating until disease stabilization and then stretching out the dosing interval?

   a. Continuous fixed dosing **b.** PRN dosing
   c. Treat and Retreat **d.** Treat and Extend

8. According to the American Academy of Ophthalmology Diabetic Retinopathy guidelines, which of the following is the initial treatment choice for centrally involved DME (CI-DME)?

   a. Panretinal photocoagulation (PRP)
   b. Intravitreal or implant corticosteroids
   c. Intravitreal anti-VEGF agents
   d. Focal laser

9. According to the American Academy of Ophthalmology Diabetic Retinopathy guidelines, which of the following is an important factor in choosing between PRP and anti-VEGF therapy for severe non-proliferative (NPDR) and proliferative DR (PDR)?

   a. Reliability of patient follow-up
   b. Location of the proliferation
   c. Insurance coverage
   d. Presence of geographic atrophy

10. In the study discussed, what was the net return on investment to society (patients and insurers) over 11 years from anti-VEGF therapies for nAMD?

    a. $5.2 billion **b.** $8.2 billion
    c. $15.0 billion **d.** $28.5 billion

Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor

1. Based on the content presented, I am better able to:

   Assess the clinical and economic burden of retinal diseases, including factors that contribute to poor prognosis and increased costs.

   4 3 2 1

   Evaluate treatment strategies and resources based on evidence for achieving the best patient outcomes in cases of retinal diseases.

   4 3 2 1

   Explain the mechanism of action, pharmacokinetics, efficacy, and dosing intervals of anti-vascular endothelial growth factor (VEGF) agents in the treatment of AMD and DME/DR.

   4 3 2 1

   Analyze current clinical guidelines and recommendations for the use of anti-VEGF therapies in AMD and DME/DR.

   4 3 2 1

   Describe how treatment innovations are improving durability, efficacy, and patient outcomes.

   4 3 2 1

   Assess medical benefit design approaches to streamline patient care to evidence-based treatments for retinal diseases.

   4 3 2 1

   Identify opportunities for managed care professionals to collaborate with other healthcare providers to improve access to care for patients with AMD and DME/DR, including addressing barriers to care such as cost, transportation, and lack of access to specialty providers.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

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   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

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GRAPHIC DESIGN
Douglas Murphy Communications

ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

JOURNAL of MANAGED CARE MEDICINE

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Retinal Diseases Monograph

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Innovative Approaches in the Treatment and Management of Retinal Diseases:

Managed Care Insights on the Evolving Role of Anti-VEGF Therapies

Jordan Graff, MD, FACS; Gary M. Owens, MD

Introduction

Neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), and diabetic macular edema (DME) are among the leading causes of vision loss in the United States (U.S.). The annual medical cost of vision loss and blindness in the U.S. has been estimated to be over $134 billion (2017 dollars).[1] This estimate included $98.7 billion in direct costs and $35.5 billion in indirect costs. The largest burden components were nursing home care ($41.8 billion), other medical care services ($30.9 billion), and reduced labor force participation ($16.2 billion), all of which accounted for 66 percent of the total. Vision loss and blindness cost an average of $16,838 incremental burden annually per person.

Beyond financial costs, there are other significant costs to vision loss. These diseases can severely impact a patient's quality of life and have a significant treatment burden for patients and their caregivers. Vision loss limits the ability to drive or perform tasks essential for maintaining independence and can lead to social isolation. Most patients require caregiver support for activities of daily living such as preparing meals and independent activities of daily living such as grocery shopping and transportation for retinal clinic treatment visits. Early detection and treatment of nAMD, DR, and DME can help improve quality of life and reduce overall costs by delaying vision loss.

Age-Related Macular Degeneration (AMD)

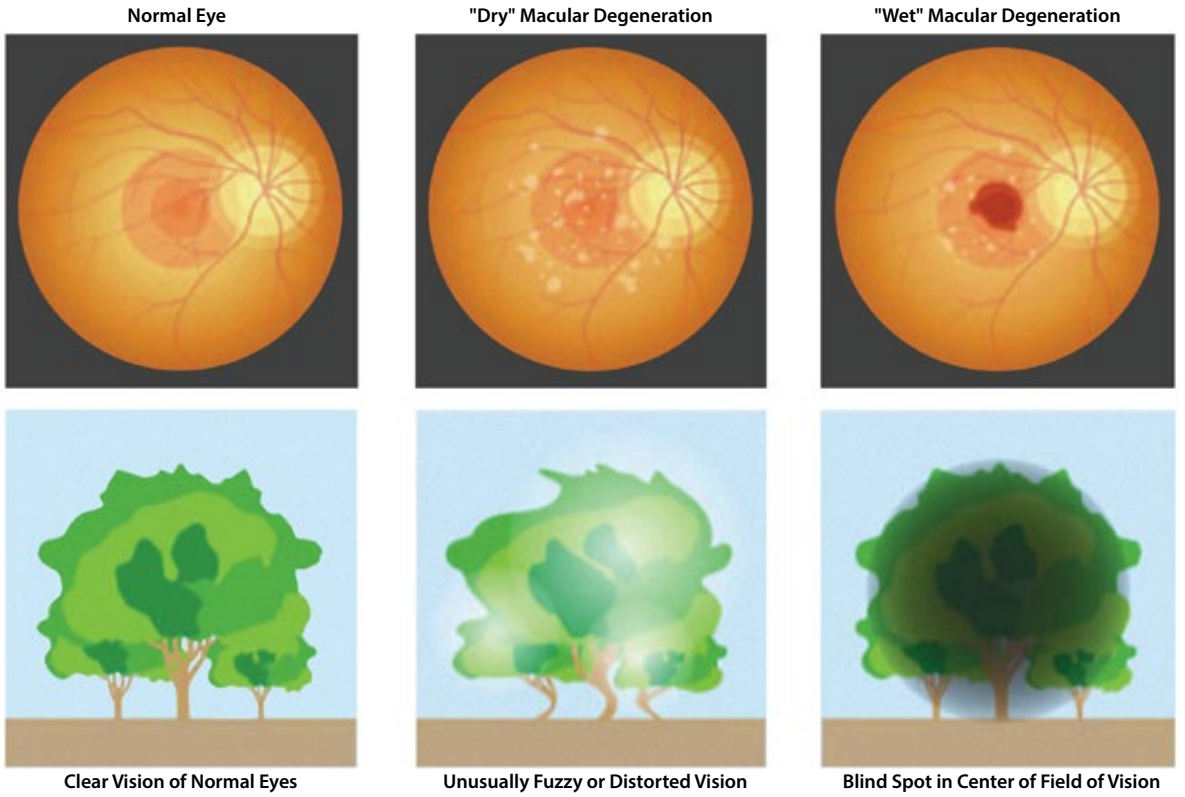
AMD results in damaged sharp and central vision, which are needed for seeing objects clearly and for reading and driving.[2] AMD affects the macula, the central part of the retina that allows the eye to see fine details. The two forms of AMD are neovascular (wet) and non-neovascular (dry) (Exhibit 1).[3] With nAMD, abnormal blood vessels behind the retina start to grow under the macula, leading to blood and fluid leakage. Bleeding, fluid, and scarring cause damage and leads to rapid central vision loss. An early symptom of nAMD is that straight lines appear wavy. The main therapeutic approach for arresting nAMD are intravitreal injections of drugs that block vascular endothelial growth factor (VEGF), which induces proliferation of vascular endothelial cells and angiogenesis.

With non-neovascular AMD, the macula thins over time as part of the aging process, gradually blurring central vision. This is the most common form of AMD accounting for 80 percent of cases but the neovascular form is responsible for 90 percent of the severe visual acuity loss (20/200 or worse) from AMD.[4] Non-neovascular AMD progresses more slowly than the neovascular form. Over time, as less of the macula functions, central vision is gradually lost. Non-neovascular AMD generally affects both eyes.

One of the most common early signs of AMD is drusen (yellow or white lipid and protein deposits under the retina). Many or large drusen are risk factors for developing AMD. The primary risk factors for the development of advanced AMD include increasing age, northern European ancestry, and genetic factors.[3] Smoking has been shown by numerous studies to be the main modifiable risk factor.

In 2019, an estimated 19.8 million (12.6%) Americans aged 40 and older were living with AMD.[5] Of these, 1.49 million (0.94%) were living with vision threatening AMD. Vision threatening AMD is also referred to as advanced or late-stage AMD and includes geographic atrophy and/or nAMD in either eye. Geographic atrophy (GA) is death of the macula cells and is the advanced stage of non-neovascular AMD. On eye exam, GA appears as a sharply demarcated, usually round, or oval, area of atrophy

Exhibit 1: Age-related Macular Degeneration[3]



of the retinal pigment epithelium not involving the center of the fovea. Prevalence of AMD increases with age from 2 percent among people aged 40 to 44 to 46.6 percent among people aged 85 and over.[5] Sex- and age-standardized rates of AMD are lower for non-Hispanic Black people (7.0%) than for other racial and ethnic groups.

The costs of care for AMD are significant with an average annual all-cause cost per patient of $24,520.[6] Outpatient costs account for 63.5 percent of the total cost and job loss or job reduction accounted for 46 percent of the cost. In a commercial claims study, significant drivers of total nAMD-related costs are anti-VEGF therapy and anti-VEGF injection frequency.[7] Anti-VEGF therapy has been the mainstay of nAMD for many years. The authors of this study concluded that the clinical and economic burden of nAMD treatment is substantial to the U.S. healthcare system, where economic burden is higher among those with active disease compared to inactive or late-stage disease (scarring). They also noted that appropriate treatment may increase the duration of inactive disease periods and preserve visual acuity while lowering overall costs.

Treatment burden is another major issue with nAMD management because frequently injected anti-VEGF agents impose a substantial time burden on patients, caregivers, physicians, and staff. There may be a need for additional support and/or reimbursement for services required by patients and caregivers and services provided by physicians. In one study, patients with nAMD treated with anti-VEGF agents accounted for 20 percent of retina specialist staff time per week.[8] In this study, an average patient visit for nAMD was 90 minutes (range: 13 minutes to more than 4 hours). When considering all their time, patients reported an average time per visit of almost 12 hours, including pre-appointment preparation (16 minutes), travel (66 minutes), waiting time (37 minutes), treatment time (43 minutes), and post-appointment recovery (9 hours). Patients stated that caregivers took time away from work (22%) and personal activities (28%) to provide transportation to appointments.

Diabetic Eye Disease

Over 38 million adults aged 18 years or older—or 14.7 percent of all U.S. adults—have diabetes.[9] Complications from diabetes like DR typically develop

Exhibit 2: DR/DME Risk Factors[11]

Category	Risk Factor
Nonmodifiable	Puberty Pregnancy
Modifiable	Hyperglycemia Hypertension Dyslipidemia Obesity
Others	Apolipoproteins: ApoB Metabolic hormones: Leptin and Adiponectin Genetic factors: HLA 3, HLA 4 Oxidative stress: Reactive oxygen species Vitamin D deficiency Local inflammatory factors

after 10 to 20 years of having the disease. Unfortunately for many with type 2 diabetes, they may have already had diabetes for many years before diagnosis.

DR is a microvascular disorder that may lead to vision-threatening damage to the retina, eventually leading to blindness. DR is classified as either non-proliferative DR (NPDR) or proliferative DR (PDR). NPDR is the early stage of DR and is characterized by the presence of microaneurysms, whereas PDR is an advanced stage of DR and can lead to severe vision loss or blindness.

DR is the most common cause of severe vision loss in working age adults in the western world and affects people with diagnosed or undiagnosed diabetes. Risk for DR is directly proportional to the patient's age and duration of diabetes, as well as glycemic, lipid, and blood pressure control.[10] DME, which can be present with any level of diabetic retinopathy, is manifested as retinal thickening caused by the accumulation of intraretinal fluid. The edema is primarily in the inner and outer plexiform layers and is believed to be a result of hyperpermeability of the retinal vasculature. DME leads to vision loss through central retinal tissue damage, foveal atrophy, epiretinal membrane damage, macular ischemia, and macular fibrosis. The modifiable and non-modifiable risk factors for DR and DME are shown in Exhibit 2.[11]

In 2021 across all ages, an estimated 9.6 million people in the U.S. were living with diabetic retinopathy (DR).[12] Of these, 1.84 million were living with vision-threatening DR. The prevalence is 77.3 percent in patients with type 1 diabetes and 25.1 percent in patients with type 2 diabetes. The prevalence rate of DR was lowest among people younger than age 25 at 13.0 percent and highest among the 65 to 79 years of age group at 28.4 percent. Non-Hispanic Black people had the highest prevalence rate of DR (3.26%) and vision-threatening DR (1.11%). The prevalence rate was higher among males than females for DR (0.64% versus 0.47%) and vision-threatening DR (2.74% versus 1.94%).

Like nAMD, DR and DME lead to significant financial and personal costs. The American Diabetes Association estimates that DR costs the U.S. around $327 billion each year. This includes $237 billion in direct medical costs and $90 billion in decreased productivity, and more than $500 million in diabetes-related blindness costs per year.[13]

Good blood glucose and blood pressure control have both been shown to reduce the risk of DR. The Diabetes Control and Complications Trial found that intensive glucose control in patients with type 1 diabetes decreases the incidence and progression of diabetic retinopathy.[14] In the UKPDS trial, the risk of retinopathy was reduced through both improved glycemic control and improved blood pressure control. A 1 percent reduction in glycosylated hemoglobin (A1C) reduced the risk for retinopathy by 31 percent and 10 mm Hg reduction in systolic blood pressure reduced photocoagulation or vitreous hemorrhage by 11 percent.[15] In addition to disease control, early detection and treatment can reduce the risk of blindness from DR by 95 percent. Unfortunately, only about 60 percent of people with diabetes have recommended yearly screenings for DR.

As DR progresses, retinal ischemia triggers the production of vasoproliferative factors such as VEGF that stimulate new vessel formation (neovascularization). The new vessels break through and grow along the surface of the retina. By themselves, these vessels rarely cause visual compromise, but they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.[16] Other angiogenic pathways such as the angiopoietin 1 (ANGPT1) and the Tie2 system modulate the effect of VEGF and directly affect retinal pericytes and endothelial cells.[17]

DME occurs because of alteration of the blood-retinal barrier which leads to pericyte loss and endothelial cell-cell junction breakdown.[18] Studies strongly indicate that DME is an inflammatory disease. Multiple cytokines and chemokines are involved in the pathogenesis of DME. With VEGF involved in both proliferative DR and DME, anti-VEGF agents have been found to be effective treatment options.

Diagnosis

AMD, DR, and DME can be identified on comprehensive eye examination. This may involve a visual acuity test, visual field testing, pupil dilation to examine the retina, Amsler grid test, fundus photography, and tonometry to measure eye pressure. Testing to confirm a diagnosis may include optical coherence tomography (OCT) which creates cross-sectional images of the retina, OCT angiography, fluorescein angiography to better examine the blood vessels of the eye, and stereoscopic biomicroscopic examination of the macula.

Treatment

The general treatment goals for AMD, DR, and DME are to slow or prevent vision loss, maintain functional vision to the greatest extent possible for the greatest duration possible, and reduce treatment burden. At each visit the patient will have a best corrected visual acuity (BCVA) test and OCT for disease monitoring and treatment efficacy.

Treatment options for DR/DME include glycemic and blood pressure control even if eyes have been previously treated, photodynamic therapy, laser treatment, surgical removal of the vitreous gel (vitrectomy), anti-VEGF therapy, and intravitreal anti-inflammatory implant or injection (DME only).[19] Options for nAMD include anti-VEGF therapy and photodynamic therapy.[4] There have been two recently approved intravitreal injected complement inhibitors indicated for the treatment of GA secondary to AMD. The use of antioxidant vitamins (i.e., vitamin C, vitamin E), lutein, zeaxanthin, and zinc in an otherwise well-nourished population with intermediate AMD has been demonstrated to reduce the progression toward more advanced stages of AMD by approximately 25 percent at five years and is recommended for patients with intermediate or advanced AMD in at least one eye.[4,20] Patients who smoke should be encouraged and supported to quit. For those with vision loss, vision aids and occupational therapy can help people live more independent lives. Because anti-VEGF therapies are the most used therapy, they will be the focus of the remaining discussion.

Anti-VEGF Therapies

Anti-VEGF therapies were first developed in the 1990s to block VEGF in the treatment of cancer. They were later found to be effective in treating ocular conditions and there are now multiple anti-VEGF therapies for eye disorders.

Bevacizumab was the first anti-VEGF agent approved by the FDA in 2004 for cancer. Since then, numerous trials have demonstrated its efficacy for various retinal diseases but it has never been FDA approved for any ocular indication. It has been used off-label for intravitreal injections for two decades. Bevacizumab is a 149 kDa recombinant humanized monoclonal antibody (mAb) comprised of two mouse antibody binding regions targeting VEGF-A, with a truncated human immunoglobulin G one (IgG1) heavy chain. It selectively binds with high affinity to all isoforms of human VEGF and neutralizes VEGF's biologic activity through a steric blocking of the binding of VEGF to its receptors (VEGFR-1, VEGFR-2). Following intravitreal injection, the binding of bevacizumab to VEGF prevents the interaction of VEGF with its receptors on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation in the retina.

Currently, bevacizumab must be repackaged in much smaller aliquots containing a small fraction of the dose used in cancer therapy. Ophthalmologists look to compounding pharmacies to create single-use vials or syringes of the appropriate dose. The process requires aseptic technique and compliance with the United States Pharmacopeia guidelines on sterile compounding. The repackaging of bevacizumab has given rise to concerns about impurities that could be introduced during the process, sterility, and dosage consistency.[21,22] Supply chain issues with bevacizumab have been and continue to be a challenge.

Some managed care plans require bevacizumab to be used before other anti-VEGF agents. The American Society of Retina Specialists and the American Academy of Ophthalmology (AAO) oppose step therapy because it increases the treatment burden on patients and creates significant administrative hurdles for retina specialists especially when the vulnerable supply chain for the repackaged drug is disrupted.[23] These two groups have been working with Medicare to remove step therapy from Medicare Advantage plans. Ophthalmologists and managed care plans must carefully consider the implications of using an off-label repackaged injection which is being introduced into the eye.

Ranibizumab is a 48 kDa recombinant mAb fragment with one VEGF-A binding site created from the same mouse antibody as bevacizumab, but lacking the fragment crystallizable (Fc) region and is small enough to avoid Fc recycling and can more easily penetrate retinal tissue.[24] It was the first agent FDA approved for ocular applications and is currently approved for intravitreal treatment of nAMD, DR, and DME. Biosimilars of the original ranibizumab reference product are now available. It is also available as a refillable intravitreal implant for AMD but this product is not currently approved for DR or DME.

The ranibizumab implant is a permanent, refillable ocular implant. It must be implanted surgically in an operating room. It is then refilled every six months in the clinic. The implant enables continuous drug delivery into the vitreous mediated by passive diffusion along a concentration gradient. This produces a more consistent ranibizumab level than intermittent injections. The implant was initially FDA approved in 2021 and the FDA issued a boxed warning for the product because it had been associated with a three-fold higher rate of endophthalmitis compared with monthly intravitreal ranibizumab injections. The manufacturer voluntarily recalled the implant after identifying that some implants did not meet pre-specified requirements which resulted in dislodgment of part of the implant. A root cause investigation revealed the leading factors contributing to septum dislodgement were insufficient bonding between the septum and overmold of the implant and excessive insertion force from the refill needle. The product was redesigned and the refill needle updated and was re-launched in summer 2024.

Aflibercept was the second agent approved for ocular indications and is FDA approved for DME, DR, and nAMD. It is a 115 kDa recombinant soluble decoy receptor with greater affinity than the natural receptors and is composed of two VEGF-binding domains, one each from VEGF-1 and VEGF-2 receptors, fused with Fc from IgG1. It traps VEGF-A, VEGF-B, and placental growth factor (PIGF) and directs them for consumption and degradation by phagocytes.[24] It may inhibit PIGF which is also associated with angiogenesis and neovascularization. Because VEGF naturally occurs as a dimer, aflibercept binds two VEGF molecules simultaneously in its two sites, creating a very high affinity interaction.[25] It is available in two strengths—8 mg, which is dosed less frequently, and 2 mg. Aflibercept 2 mg was FDA approved in November 2011 and aflibercept 8 mg was approved in August 2023. Comparison trials of the 8 mg and 2 mg formulations are discussed later under each disease category.

Brolucizumab is a 26 kDa humanized monoclonal single-chain variable fragment. It binds VEGF-A with a single binding site in a 2:1 brolucizumab:VEGF ratio.[24] It is FDA approved for nAMD and DME with studies for the treatment of DR underway. One issue with this agent is the increased risk of intraocular inflammation compared to other anti-VEGF agents, thus, use of this agent has been low.

Faricimab is a dual-mechanism antibody with two different antigen-binding fragment regions, one which targets VEGF and the other targeting Ang-2.[24] The FDA approved it for nAMD and DME in 2022. Studies of faricimab for the treatment of DR are underway.

Comparing the Agents

Intravitreal administration of anti-VEGF antibodies have become the standard treatment for DME, DR, and nAMD. Each of the agents have shown sufficient benefit for their FDA-approved indications. As each agent has been approved, it has typically been compared to an earlier product. For example, in nAMD, ranibizumab was studied against bevacizumab, aflibercept 2 mg against ranibizumab, and brolucizumab and faricimab against aflibercept 2 mg.

The knowledge of their pharmacokinetics in the eye is limited because it is very difficult to perform intravitreal pharmacokinetic studies on humans. Taking vitreous samples is an invasive procedure and therefore, most of the studies have focused on preclinical research. The pharmacokinetic studies center on the half-lives of the anti-VEGF drugs in different compartments (vitreous, aqueous humor or serum).[26] Example intravitreal half-lives include 4.7 days for aflibercept 2 mg, 2.9 for ranibizumab, and 4.3 days for bevacizumab.[27] The intravitreal injections are typically started once monthly but this interval can be extended out for some agents as discussed later.

Treatment Guidelines in DR/DME

Exhibit 3 provides an overview of the benefits of anti-VEGF therapy in DR.[24] The American Academy of Ophthalmology (AAO) guidelines provide recommendations for when various therapeutic options are appropriate in initially managing DR with or without DME (Exhibit 4).[19] Anti-VEGF therapy is the initial treatment choice for centrally involved DME (CI-DME), with possible subsequent focal laser treatment for persistent edema.[19] The AAO guidelines note that a key clinical consideration for determining the use of anti-VEGF versus panretinal photocoagulation (PRP) for severe non-proliferative (NPDR) and proliferative DR (PDR) is reliability of patient follow-up. One analysis found that over a four-year period, 22 percent of patients with PDR under treatment with anti-VEGF injections were lost to follow-up. Recent data suggests that in patients with PDR, anti-VEGF is superior to PRP in terms of visual acuity benefit, DME prevention, adverse effect of visual field loss, and the need for future laser treatment.[24] A meta-analysis of five studies on 632 eyes found that on average, anti-VEGF intervention in patients with PDR resulted in an additional four letters gained compared with PRP at 12 months, and the difference was statistically significant.[28] The complication profile was also more favorable with anti-VEGF over PRP, with a 10 percent absolute risk reduction in the need for future vitrectomy and a 10 percent absolute risk reduction in vitreous hemorrhage rates.

Exhibit 3: Evidence for Use in Diabetic Retinopathy[24]

Stage of Diabetic Retinopathy	Application of Anti-VEGF Therapy	Evidence-Based Benefits	Level of Evidence
Mild nonproliferative DR	None	• N/A	N/A
Moderate–severe nonproliferative DR	Primary monotherapy	• Prevention of PDR. • Prevention of DME. • Prevention of DRSS worsening.	Phase III trials: DRCR Protocol W and PANORAMA.
Proliferative DR	Primary monotherapy	• Prevention of DRSS worsening. • Prevention of DME.	Phase III trial: RECOVERY.
	Alternative to PRP	• Fewer complications. • More ETDRS letters gained. • Reduced risk of future hemorrhage. • Reduced need for future vitrectomy.	Meta-analysis, multiple RCTs.
	Adjunct to PRP	• Better clinical outcomes compared to PRP alone. • Reduced degree of follow-up burden compared with anti-VEGF therapy alone. • Prevention of the need for additional PRP treatments, reduced adverse ocular events.	Post hoc analyses of Phase III RIDE and RISE trials, several small trials.
	Adjunct to pars plana vitrectomy	• Less intraoperative bleeding and need for endodiathermy. • Reduced rates of iatrogenic retinal breaks. • Reductions in surgical times • Superior visual acuity up to at least 6 months. • Shorter time to vitreous clearance. • Lower rates of postoperative hemorrhage. • Decreased likelihood of developing new CI-DME. • Decreased risk of new tractional retinal detachment.	Meta-analysis, multiple RCTs.

PDR = proliferative diabetic retinopathy; DME = diabetic macular edema; DRSS = diabetic retinopathy severity scale; ETDRS = Early Treatment Diabetic Retinopathy Study; PRP = panretinal photocoagulation

The AAO guidelines do not recommend any specific anti-VEGF treatment for DR or DME.[19] One prospective comparative trial of aflibercept 2 mg, bevacizumab, and ranibizumab in DME has been published.[29] The primary outcome was the mean change in visual acuity at one year. Intravitreal aflibercept 2 mg, bevacizumab, or ranibizumab improved vision in eyes with CI-DME. When the initial visual-acuity loss was mild, there were no apparent differences between the three agents. At worse levels of initial visual acuity (≥ 20/50), aflibercept 2 mg was more effective at improving vision in one year. At two years, aflibercept 2 mg was only better than bevacizumab. Faricimab has been compared to aflibercept 2 mg for DME.[30] This trial used faricimab 6 mg every eight weeks, faricimab 6 mg treat and extend (T and E, up to 16 weeks), or aflibercept 2 mg every eight weeks. Noninferior year one visual acuity gains were maintained through year two; mean BCVA change from baseline at two years with faricimab every eight weeks (YOSEMITE and RHINE, +10.7 letters and +10.9 letters, respectively)

Exhibit 4: American Academy of Ophthalmology Initial Management Recommendations for Diabetic Retinopathy with or without Diabetic Macular Edema[19]

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	NCI-DME	3 – 6	No	Sometimes	No
	CI-DME**	1	No	Rarely	Usually
Moderate NPDR	No	6 – 12	No	No	No
	NCI-DME	3 – 6	No	Sometimes	Rarely
	CI-DME**	1	No	Rarely	Usually
Severe NPDR	No	3 – 4	Sometimes	No	Sometimes
	NCI-DME	2 – 4	Sometimes	Sometimes	Sometimes
	CI-DME**	1	Sometimes	Rarely	Usually
Non-high risk PDR	No	3 – 4	Sometimes	No	Sometimes
	NCI-DME	2 – 4	Sometimes	Sometimes	Sometimes
	CI-DME**	1	Sometimes	Sometimes	Usually
High risk PDR	No	2 – 4	Recommended	No	Sometimes
	NCI-DME	2 – 4	Recommended	Sometimes	Sometimes
	CI-DME**	1	Recommended	Sometimes	Usually

* Adjunctive intravitreal corticosteroids or anti-VEGF agents may be considered. Off-label except for aflibercept and ranibizumab
** Defer treatment until visual acuity worse than 20/25 with some exceptions
NPDR = non-proliferative diabetic retinopathy ; PDR = proliferative diabetic retinopathy ; DME = diabetic macular edema;
NCI = non center involved ; CI = center involved.

or T and E (+10.7 letters and +10.1 letters, respectively) were comparable with aflibercept 2 mg every eight weeks (+11.4 letters and +9.4 letters, respectively). Mean CST reductions were greater, more patients achieved absence of DME (CST < 325 µm), and absence of intraretinal fluid with faricimab every eight weeks or T and E versus aflibercept 2 mg every eight weeks through year two.

Brolucizumab 6 mg every eight to 12 weeks or aflibercept 2 mg every eight weeks were compared in DME in a Phase III trial.[31] At Week 52, brolucizumab 6 mg was noninferior to aflibercept 2 mg in mean change in BCVA from baseline (+ 10.6 letters versus + 9.4 letters; $p < .001$), more subjects achieved central subfield thickness (CSFT) < 280 µm, and fewer had persisting subretinal and/or intraretinal fluid versus aflibercept 2 mg, with more than half of brolucizumab 6 mg subjects maintained on q12w dosing after loading. The incidence of ocular serious adverse events was 2.2 percent (brolucizumab 6 mg) and 1.7 percent (aflibercept 2 mg). Brolucizumab is typically reserved for when patients with DME fail to achieve drying with other anti-VEGF agents.

The aflibercept 8 mg formulation has been compared to the standard 2 mg formulation dosing in a randomized, double-masked, non-inferiority, Phase II/III trial performed at 138 hospitals and specialty retina clinics in seven countries in patients with central DME (PHOTON).[32] The three treatment groups were aflibercept 2 mg every eight weeks (2q8), aflibercept 8 mg every 12 weeks (8q12), or aflibercept 8 mg every 16 weeks (8q16), following initial monthly dosing. From week 16, dosing intervals for the aflibercept 8 mg groups were shortened if patients met prespecified dose regimen modification criteria denoting disease activity. The primary endpoint was change from baseline in BCVA at week 48 (non-inferiority margin of 4 letters). Aflibercept 8q12 and 8q16 were non-inferior to aflibercept 2q8 for BCVA gains (BCVA mean change from baseline 8.8 letters [SD 9.0] in the 8q12 group, 7.9 letters [8.4] in the 8q16 group, and 9.2 letters [9.0] in the 2q8 group). The difference in least

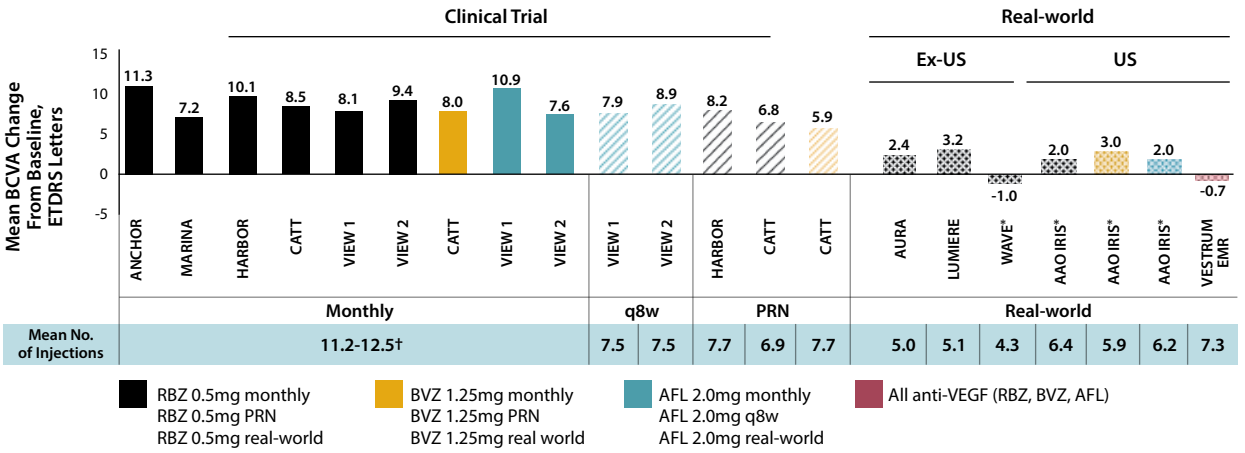
Exhibit 5: Trials Comparing Faricimab and Brolucizumab to Aflibercept 2 mg[39-41]

Design	Agents/Dosing	Results
Two Phase III randomized, double-masked, non-inferiority trials across 271 sites worldwide Treatment-naïve patients with nAMD aged ≥ 50. TENAYA N = 671 LUCERNE N = 658	Faricimab 6 mg up to every 16 weeks versus Aflibercept 2 mg every 8 weeks	BCVA change from baseline was non-inferior. TENAYA (faricimab adjusted mean change 5.8 letters [95% CI 4.6 to 7.1] and aflibercept 5.1 letters [3.9 to 6.4]; treatment difference 0.7 letters [-1.1 to 2.5]). LUCERNE (6.6 and 6.6; treatment difference 0.0 [-1.7 to 1.8]) Rates of ocular adverse events were comparable between faricimab and aflibercept (36.3% versus 38.1%, and 40.2% versus 36·2%).
Two Phase III, double-masked, multicenter, non-inferiority, randomized trials. HAWK, HARRIER N = 1,817	Brolucizumab 6 mg every 8 to 12 weeks versus Aflibercept 2 mg every 8 weeks. [HAWK included a 3 mg brolucizumab group but this dose is not FDA approved so data not included).	At Week 48, noninferiority in BCVA change from baseline (least squares [LS] mean, +6.6 letters with brolucizumab versus +6.8 letters with aflibercept [HAWK]; +6.9 versus +7.6 aflibercept [HARRIER]; $p < 0.001$ for each comparison). > 50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing through week 48 (56% and 51%). Better outcomes regarding retinal fluid and retinal thickness with brolucizumab 6 mg versus aflibercept at weeks 16 and 48. Serious adverse ocular events – brolucizumab 3.1% and 2.4% versus aflibercept 0.8% and 1.1%.
Multicenter, randomized, double-masked Phase IIIa study Recalcitrant nAMD (persistent residual retinal fluid despite previous frequent anti-VEGF. MERLIN N = 535	Brolucizumab 6 mg every 4 weeks versus Aflibercept 2 mg every 4 weeks	Brolucizumab noninferior to aflibercept 2 mg in mean BCVA change from baseline to week 104 (treatment difference 0.4 letters). Proportion of eyes with ≥ 15-letter loss was 6.2% for brolucizumab and 4.7% for aflibercept ($p = 0.0014$). Greater proportion of eyes were fluid free at week 104 (52.5% brolucizumab versus 28.2% aflibercept; 95% CI, 11.9-37.3; $p < 0.001$). Incidence of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, was 11.5% (0.8% and 2.2%) for brolucizumab versus 6.1% (0% and 0.6%) for aflibercept, respectively.

squares means was -0.57 letters between 8q12 and 2q8 and -1.44 letters between aflibercept 8q16 and 2q8. Ocular adverse events were similar across groups (8q12, 32%; 8q16, 29%; 2q8, 28%).

Three-year (156-week) data from an extension study of the PHOTON trial showed the vast majority of aflibercept 8 mg patients (88%) who entered the extension study sustained the visual gains and

Exhibit 6: Real-world One-year Visual Acuity Outcomes Fall Short of Clinical Trial Results[36,37,45-53]



*BCVA data reported in logMar; conversion calculated using 0.02 logMar = 1 ETDRS letter.
†Includes reported data and estimated data based on month treatment.
AFL = aflibercept; BCVA = best-corrected visual acuity; BVZ = bevacizumab; ETDRS = Early Treatment Diabetic Retinopathy Study; LogMar = logarithm of the minimum angle of resolution; PRN = as-needed; RBZ = ranibizumab; q8w = every 8 weeks; VEGF = vascular endothelial growth factor.

anatomic improvements achieved by the end of the second year, while achieving substantially longer treatment intervals than have been previously demonstrated. Additionally, patients switched from 2 mg to 8 mg dosing experienced substantially slower fluid reaccumulation. This data was presented recently at the 2024 American Academy of Ophthalmology Annual Meeting but has not yet been published.[33] The achievement of non-inferiority with much longer dosing intervals, similar safety, and notably slower fluid reaccumulation with the 8 mg formulation suggests that this formulation could decrease treatment burden with equivalent outcomes in those with DME.

Only ranibizumab and aflibercept 2 and 8 mg are FDA approved for treating DR. A Cochrane review of 12 studies utilizing bevacizumab, ranibizumab, and aflibercept 2 mg found no differences in visual acuity in subgroup analyses comparing the type of anti-VEGFs, the severity of the disease, time to follow-up (less than 12 months versus 12 or more months), and treatment with anti-VEGFs in combination with PRP versus anti-VEGFs alone.[34] The review also concluded that anti-VEGFs with or without PRP compared with PRP alone probably increase visual acuity, but the degree of improvement is not clinically meaningful. For secondary outcomes, anti-VEGFs with or without PRP produce a regression of new vessels, reduce vitreous hemorrhage, and may reduce the need for vitrectomy compared with eyes that received PRP alone. Aflibercept 2 mg has also been studied against placebo in one trial for severe NPDR.[35] Over a year, aflibercept 2 mg either every eight or 16 weeks produced better improvement in diabetic retinopathy severity scale (DRSS) scores and reduced risk of developing CI-DME or other vision-threatening complications.

Treatment Guidelines in nAMD

The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies for the treatment of nAMD. According to the AAO guidelines, anti-VEGF therapy is first-line for treating and stabilizing most cases of nAMD.[4] Similar to DR, these guidelines do not recommend a specific anti-VEGF agent and faricimab nor aflibercept 8 mg are yet included in the guidelines.

Numerous comparative trials of anti-VEGF agents have been done in nAMD. A Cochrane review (2019) concluded that ranibizumab and bevacizumab improved visual acuity and were equally effective.[36] A meta-analysis (2018) found that bevacizumab and ranibizumab had equivalent efficacy for best corrected visual acuity (BCVA), whereas ranibizumab had greater reduction in central macular thickness, and aflibercept 2 mg and ranibizumab had comparable efficacy for BCVA and central macular thickness.[37] A Cochrane review (2016) of aflibercept 2 mg found comparative effectiveness of aflibercept 2 mg versus ranibizumab for visual acuity and morphological outcomes in eyes with nAMD.[38] More recent trials have found faricimab and brolucizumab to be

non-inferior to aflibercept 2 mg (Exhibit 5).[39-41] No published trials with aflibercept 8 mg compared to faricimab or brolucizumab have been identified. Brolucizumab has not been frequently used but one role may be for use in those who have failed other anti-VEGF based on the Merlin trial.[40]

Since these reviews and trials, aflibercept 8 mg has become available for nAMD (and other indications) which has a reduced administration frequency. In the PULSAR trial, adults with nAMD were randomized 1:1:1 to aflibercept 8 mg every 12 weeks (8q12), aflibercept 8 mg every 16 weeks (8q16), or aflibercept 2 mg every eight weeks (2q8), following three initial monthly doses in all groups.[42] From week 16, patients in the aflibercept 8 mg groups had their dosing interval shortened if pre-specified dose regimen modification criteria denoting disease activity were met. Change from baseline in BCVA at week 48 was the primary endpoint. In over 1,000 patients (aflibercept 8q12 n = 335; aflibercept 8q16 n = 338; and aflibercept 2q8 n = 336), aflibercept 8q12 and 8q16 showed non-inferior BCVA gains versus aflibercept 2q8 (mean BCVA change from baseline +6.7 [SD 12.6] and +6.2 [11.7] versus +7.6 [12.2] letters). Mean BCVA changes were sustained out to week 96 and continued to be non-inferior. The least squares mean differences between aflibercept 8q12 versus 2q8 and 8q16 versus 2q8, respectively, were -0.97 and -1.14 letters (non-inferiority margin at 4 letters). In terms of secondary outcomes, no statistically significant difference in least square mean change in central subfield thickness at 48 and 96 weeks was seen among the three groups. The mean number of injections were substantially lower in the 8q12 and 8q16 groups compared to 2q8 group over 96 weeks (9.7, 8.2, 12.8, respectively). Eighty-seven percent of the 8q12 group and 79 percent of the 8q16 was able to maintain that dosing interval or better at 96 weeks. Importantly, 31 percent of the 8q12 and 48 percent of 8q16 were able to have their dosing intervals extended out to 20 weeks or longer. The incidence of ocular adverse events in the study eye was similar across groups (8q12, 39%; 8q16, 38%; 2q8, 39%). The use of aflibercept 8 mg at extended dosing intervals with comparative efficacy and safety to 2 mg dosing will improve the management of patients with nAMD.

A small trial (n = 108) comparing aflibercept 8 mg to 2 mg found trends in anatomic and visual improvements over 44 weeks with aflibercept 8 mg which suggest additional therapeutic benefit.[43] The proportion of eyes without fluid in the central subfield with 8 mg versus 2 mg aflibercept was 50.9 percent (n = 27) versus 34.0 percent (n = 18) (difference, 17.0 [95% CI, -1.6 to 35.5] percentage points; p = .08) at week 16 and 39.6 percent (n = 21) versus 28.3 percent (n = 15) (difference, 11.3 [95% CI, -6.6 to 29.2] percentage points; nominal p = .22) at week 44. At week 44, mean (SE) change in central retinal thickness was -159.4 (16.4) versus -137.2 (22.8) µm with 8 mg versus 2 mg of aflibercept, respectively (least squares mean difference, -9.5 [95% CI, -51.4 to 32.4]; nominal p = .65) and mean (SE) change in best-corrected visual acuity score was +7.9 (1.5) versus +5.1 (1.5) letters (least squares mean difference, +2.8 [95% CI, -1.4 to +7.0]; nominal p = .20). No differences in safety profiles between the groups were observed. These differences in anatomical outcomes suggest possible differences in outcomes with aflibercept 8 mg compared to aflibercept 2 mg. More data are needed to make a definitive decision.

Real-World Outcomes for DME and nAMD

Real-world outcome studies have demonstrated that patients do not always achieve the same benefits shown in clinical trials. A chart review study of anti-VEGF therapy used for DME in 156 patients at 10 sites who received three or more anti-VEGF injections (ranibizumab, bevacizumab) found that the mean number of anti-VEGF injections fall off over time (5.8 in Year 1, 5.0 in Year 2, and 3.4 in Year 3).[44] Additionally, many patients did not achieve 20/40 or better visual acuity and/or a dry macula after anti-VEGF injection.

In nAMD, real-world one-year visual acuity outcomes with anti-VEGF therapies also fall short of clinical trial results (Exhibit 6).[36,37,45-53] Similar to DME, this data appears to show that fewer injections are being done in the real-world and may account for at least some of the significant difference in visual acuity outcomes. Longer-term data show that injection frequency and visual acuity continue to decline. An analysis of six years of data from the Intelligent Research in Sight (IRIS) Registry found a mean visual acuity increase of 3.0 letters at year one but annual decreases led to a net loss from baseline of 4.6 letters after six years.[54] Patients with longer follow-ups had better baseline and follow-up visual acuity. From a mean of 7.2 in year one and 5.6 in year two, mean injections plateaued between 4.2 to 4.6 in years three through six. Importantly, every additional injection resulted in a 0.68 letter improvement from baseline to year one, thus, multiple injections in a year have the potential to be clinically meaningful. Older age, male gender, Medicaid insurance, and not being treated by a retina specialist were associated with a higher likelihood of vision loss at year one. Real-world data on the afilibercept 8 mg, ranibizumab implant, faricimab, and brolucizumab which have longer dosing intervals are not yet available.

Treatment Guidelines for Non-neovascular AMD

The AAO guidelines recommend that treatment with antioxidants and minerals as described in the original AREDS and AREDS2 trials should be considered for patients who have progressed to intermediate or advanced non-neovascular AMD in at least one eye.[4] Geographic atrophy when present leads to classification of intermediate or advanced AMD. GA can occur with or without neovascularization. Two complement inhibitors (avacincaptad pegol and pegcetacoplan) have been approved by the FDA for treating GA. Avacincaptad pegol is injected every 25 to 60 days and pegcetacoplan every month. A Cochrane review of these agents noted that these agents reduce GA lesion growth at one year but there is currently no evidence that complement inhibition with any agent improves functional endpoints in advanced AMD.[55] Further results from the Phase III studies may better define the benefits of these agents. The cost of these two injections is similar to that for the anti-VEGF agents.

Adherence Issues

A primary challenge of VEGF inhibitor therapy is the need for repeated intravitreal injections which contributes to nonadherence, undertreatment, and high discontinuation rates. In a retrospective cohort study of DME patients, the discontinuation rate among the 1,702 eligible patients from 24 to 60 months after treatment initiation was 30 percent.[56] In the IRIS Registry nAMD study previously discussed, treatment was discontinued in 38.8 percent.[54]

To improve adherence with anti-VEGF treatments, clinicians have tried a Treat and Extend (T and E) paradigm. Initially the patient is treated monthly until disease activity stabilization and then the treatment interval is gradually extended in increments of two to four weeks, up to a maximum interval of 12 to 16 weeks based on response. Treatment intervals are shortened when disease activity recurs. There is a growing body of evidence supporting the T and E regimens which offers the promise of comparable visual and anatomical outcomes while reducing injection burden. A metanalysis comparing T and E with fixed or as needed (PRN) regimens for CI-CME found that visual acuity improvement was similar at 12 and 24 months.[57] Regarding anatomic outcomes, no significant difference was found between T and E and fixed regimens for central retinal thickness or central subfoveal thickness at 12 and 24 months. Similarly, no significant difference was found for central retinal thickness at 12 months for T and E versus PRN regimens. Another meta-analysis only examining outcomes through one year found different results. In this analysis T and E for DME did not show a clear advantage in reducing the number of injections compared to landmark clinical trials with PRN treatment regimens in the first year of treatment with limited gains in visual and anatomical outcomes.[58] The difference in the two analyses may be the focus on number of injections compared with the visual and anatomic outcomes. Clinically meaningful visual acuity gains from baseline, anatomic improvements, and extended durability in DME have been shown with afilibercept 8 mg T and E up to 16 weeks through three years, faricimab T and E up to every 16 weeks through two years and with brolucizumab T and E up to 12 weeks.[33,59,60]

In nAMD, a meta-analysis of trials found that visual acuity (VA) improvement was similar with T and E and fixed dosing at one (mean difference -0.08 letters, $p = 0.95$) and two years (0.58 letters, $p = 0.62$).[61] In contrast, VA improvements were significantly greater for T and E when compared against a PRN regimen at one (3.95 letters, $p < 0.0001$) and two years (4.08 letters, $p < 0.001$). Significantly fewer ranibizumab injections were administered in the T and E arm at one (-2.42 injections, $p < 0.0001$) and two years (-6.06 injections, $p < 0.00001$) relative to fixed dosing. Fewer aflibercept injections were likewise administered to patients on a T and E regimen versus fixed dosing at one year (-0.78 injections, $p < 0.0001$). The authors concluded that low-certainty evidence from the present synthesis implies that T and E preserves VA similar to fixed schedules with significantly fewer injections at one and two years. Patients with T and E dosing achieved better VA outcomes than those on PRN regimen but T and E dosing was associated with more injections. Additional aflibercept T and E trials using 2 mg out to 12 weeks and 8 mg dosing for 12 to 16 weeks have been published since this analysis which show similar findings.[42,43]

No specific T and E studies were found using anti-VEGF therapy for DR. Only ranibizumab and aflibercept 2 and 8 mg are FDA approved for this indication. The package labeling for each agent does indicate dosing intervals can be extended without specifying a particular indication.[62,63]

Overall, T and E is the preferred option for most clinicians because it allows the extension of intravitreal injection treatment intervals while reducing the overall number of clinic visits. Longer interval dosing regimens reduce patient, caregiver, and provider treatment burden in comparison with monthly dosing regimens and may reduce risk associated with frequent injections.[38] Data to date does not indicate a significant difference in visual or anatomic outcomes with intravitreal injection T and E compared to fixed and PRN dosing intervals.

Cost Utility and Effectiveness

Anti-VEGF therapies are expensive with retail cost of $1,000 to $2,500 per injection but have several benefits, including patient benefit, societal value, and cost effectiveness. One study found that improved vision from anti-VEGF therapies (current treatment scenario of less frequent injections) used for nAMD in the over 65 years of age population generated $1.1 billion in patient benefit for the full population in year one and $5.1 billion in year three, whereas the scenario of more frequent injections generated $1.6 billion (year 1) and $8.2 billion (year 3).[64] Three-year benefits ranged from $7.3 billion to $11.4 billion with improved adherence and from $9.7 billion to $15.0 billion if 100 percent of the patients initiated anti-VEGF treatment and the discontinuation rates were 6 percent per year or equivalent to clinical trial discontinuation (best-case scenario). Societal value (patient benefits net of treatment cost) ranged from $0.9 billion to $3.0 billion across three years in the current treatment scenarios and from $0.9 billion to $4.3 billion in the treatment innovation scenarios. Another study found that anti-VEGF therapy for nAMD produced a net return on investment $28.5 billion to society (patients and insurers) over 11 years and contributed $12.2 billion to the Gross Domestic Product over those years.[65]

In terms of cost effectiveness, an analysis based on published clinical trial data for aflibercept 2 mg preventing progressive DR (PDR or CI-DME) found the cost required to prevent one case of PDR was $80,000 in a hospital-based facility and $72,400 in a non-hospital setting (Medicare costs).[66] To prevent one case of CI-DME with vision loss, the cost was $154,000 and $133,000, respectively. For all CI-DME, with and without vision loss, the costs to prevent a case were $70,900 and $59,500 for aflibercept 2 mg every 16 weeks and $90,000 and $88,800 for 2 mg every eight weeks PRN. The cost per unit change in DRSS was $2,700 and $2,400/DRSS over two years.

Payer Management

The global intravitreal anti-VEGF market size was valued at $22.9 billion (U.S. dollars) in 2022.[67] It is projected to grow to $33.4 billion by 2032. Anti-VEGF drugs are among the most expensive drugs for Medicare at an annual cost of $4.02 billion in 2019.[68] Increased screening rates result in more patients being diagnosed with retinal diseases and an aging overweight population prone to AMD and diabetic eye disease are the key market drivers enhancing the market growth.

Step edits and bevacizumab first policies are common. Most payers require prior authorization on branded agents, but not on bevacizumab. These medications are covered under the medical benefit, so formulary tiers typically do not apply. Few payers have preferred branded agents in this category. The impact of biosimilars needs to be considered going forward in addition to off-label use of bevacizumab. There are currently two ranibizumab biosimilars but despite lower costs ($869 and $1,130 per dose compared to $1,850) their uptake was low in the first year of availablity.[69] At least eight aflibercept biosimilars are in the pipeline. New approaches such as T and E are generally not incorporated in payer policies. Additionally, managed care will have to contend with the new agents for geographic atrophy and which patients are appropriate candidates.

Future Therapies

There is an investigational ophthalmic formulation of bevacizumab under development to be administered as an intravitreal injection for the treatment of nAMD and other approved retinal diseases (ONS-5010 /bevacizumab-vikg). If FDA approved, ONS-5010 will replace the need to use off-label repackaged IV bevacizumab from compounding pharmacies for the treatment of nAMD. It has already been approved in the European Union (May 2024). Oral fenretinide, a synthetic derivative of all-trans-retinoic acid, is being developed to slow the progression of geographic atrophy.[70] Sozinibercept in combination with standard-of-care anti-VEGF therapies is being studied in nAMD and DME. Sozinibercept is a soluble form of VEGFR-3 expressed as an immunoglobulin G1 Fc-fusion protein which binds and neutralizes the activity of VEGF-C and VEGF-D on their endogenous receptors, VEGFR-2 and VEGFR-3.

Gene therapy is also under investigation. Two different methods of delivery are being studied. One injects the gene therapy underneath the retina in a surgical procedure and the other injects it into the eye just like a routine anti-VEGF treatment and is done in the ophthalmologist's office.

Another concept under investigation is the possibility of replacing cells that begin to die in late-stage non-neovascular AMD. Transplanted stem cells may be able to replace the retinal cells that are killed off by this disease. One strategy is to layer the stem cells on thin scaffolds. Another tactic is to put the cells into a fluid suspension that can be injected under the retina. It may take about 10 to 15 years for these therapies to be fine-tuned and prove effective in humans.

Conclusion

There are significant costs to vision loss, so prompt intervention with anti-VEGF agents is necessary to prevent deterioration of visual acuity and to prevent blindness in nAMD, DR, and DME. Patients

benefit most when adherence is optimized, but in the real-world adherence is sub optimal. Newer approaches such as treat and extend may be one way to improve adherence and not compromise outcomes. Additionally, these patients are affected by social determinants and may require additional support to obtain optimal outcomes. Payer policies need to evolve to take these factors into consideration.

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