SPECIAL ARTICLE

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Recent Updates on the Diagnosis and Management of Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the Western world, with a higher prevalence among Europeans and North Americans than that in Africans, Hispanics, and Asians. Advanced AMD is categorized as atrophic (dry) or exudative (wet/neovascular age-related macular degeneration [nAMD]). Dry AMD is characterized by progressive geographic atrophy of the retinal pigment epithelium and outer retinal layers, whereas nAMD is characterized by new vessels that invade the subretinal and/or subretinal pigment epithelium spaces. Existing treatments delay the onset of advanced AMD and reverses vision loss for a couple of years before atrophy usually decreases central visual acuity. We searched PubMed and Medline databases from January 1, 1980, to December 1, 2023, using the following search terms: *macular degeneration, choroidal neovascularization, geographic atrophy, drusen, age-related maculopathy, AMD, ARMD, and anti-VEGF*. Relevant articles in English (or English translations) were retrieved and reviewed. Bibliographies of the identified manuscripts were also reviewed to identify relevant studies. Age-related macular degeneration most commonly affects people older than 55 years. Visual prognosis varies, with advanced lesions (nAMD and geographic atrophy) leading to rapid, progressive loss of central vision and contrast sensitivity. Although AMD is not a life-threatening disease, reduced vision profoundly compromises quality of life and necessitates living assistance for many patients. Over the past 2 decades, advances in prevention (vitamin supplementation) and therapy (antivascular endothelial growth factor and complement inhibitor drugs) have reduced vision loss and blindness. Further research is needed to decrease the incidence of blindness in patients with advanced disease.

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Advances in medical care and public health over the past century have prolonged life expectancy throughout the world and significantly increased the number of people aged 60 years or older. As a result, the number of health problems attributed to age-related maculopathies have skyrocketed. Most important among them, age-related macular degeneration (AMD) is a multifactorial, sight-threatening disease that is the fourth most common cause of blindness worldwide.[1] Patients with early stage AMD may be asymptomatic, but many of them progress to advanced AMD with loss of central vision due to new vessels (wet or neovascular age-related macular degeneration [nAMD]) that bleed or leak fluid into the macula (the central 6 mm of the retina) or choroid or from the development of geographic atrophy (GA) with death of photoreceptors and retinal pigment epithelium (RPE) cells (the pigmented monolayer forming the outer boundary of the retina).

Costs attributed to AMD—direct costs from the medical care of affected patients and indirect costs from lost wages, transportation expenses, and supportive home care needs—are substantial and increasing rapidly. Age-related macular degeneration diminishes patients' quality of life and increases the risk of functional disability. Patients with AMD report lower levels of activity, higher incidences of depression, and elevated stress compared with their peers without AMD.[2] Only limited treatments are available for early AMD but preventing or slowing its

progression could reduce the burden on the health care system and improve the quality of life of tens of thousands of individuals.

Considering the high prevalence of AMD in the community and the likelihood that this will continue to increase into the foreseeable future, general physicians will benefit from an improved understanding of the disease, its epidemiology, prognosis, and treatments. Knowing which treatments have been tried (and abandoned) and which have become standard of care allows physicians to better counsel their patients. The aim of this study was to provide a comprehensive overview of AMD tailored to the needs of the primary care physician.

EPIDEMIOLOGY

Nearly 200 million people throughout the world have some form of AMD,[3] with more than 20 million of them in the United States (2019),[4] numbers that are expected to increase over the next decades. The prevalence of AMD is increasing in sync with the aging population, and the projected number of persons with AMD throughout the world is expected to increase from 196 million in 2020 to 288 million in 2040.[3] Age-related macular degeneration has become the leading cause of irreversible central vision loss in individuals older than 50 years in industrialized nations,[5] with reported prevalence of 12.33% in Europe, 7.38% in Asia, and 7.50% in Africa.[3] Age-related macular degeneration has been consistently found to be more prevalent among Whites than that in Blacks.[6-9]

Dry AMD (drusen fatty deposits within Bruch membrane, pigmentary changes, and RPE atrophy) accounts for 85%-90% of all cases; although wet or nAMD is responsible for only 10%-15% of cases,[7,8] it accounts for 90% of AMD-related blindness. Because 42% of patients with nAMD in 1 eye develop neovascular membranes in the second eye within 5 years,[9] a patient with nAMD in 1 eye who develops suggestive symptoms (blurred vision or distortion) in the fellow eye should be referred promptly.

PATHOPHYSIOLOGY

Age-related macular degeneration is a multifactorial disease, the etiology of which is not completely understood, but RPE dysfunction due to oxidative stress, lipid metabolism, inflammation, and complement activation is believed to play a crucial role. The elevated metabolic rate and high oxygen consumption of the macula puts this tissue in a state of chronic oxidative stress.[10] The continuous uptake and degradation of shed photoreceptor outer segments by the adjacent, aging RPE cells causes lipofuscin to accumulate beneath the retina, which induces cell injury, dysregulation of RPE function, and abnormal extracellular matrix deposition into Bruch membrane (the basement membrane of both the RPE and the choriocapillaris [the innermost blood vessel layer of the choroid]). Together with oxidative stress, these changes trigger inflammation that damages the RPE and compromises the outer blood-retinal barrier (the tight junctions between RPE cells that limit albumin movement into the retina).[11] Progressive damage to Bruch membrane together with the upregulation of vascular endothelial growth factor (VEGF) due to hypoxia and inflammation induces the growth of new choroidal vessels into the sub-RPE or subretinal spaces.

Excessive activation of complement, present in high concentration within drusen, contributes to disease progression.[12,13] Oxidative stress amplifies this response by making the RPE more susceptible to complement-associated injury. Activation of the complement cascade together with oxidative stress increase VEGF secretion by up to 100-fold, thereby inducing abnormal new vessel formation in the macula (macular neovascularization [MNV]).

Genetic, environmental, and metabolic factors play complex roles in the development of AMD. The most important nonmodifiable risk factors are advanced age,[14,15] Caucasian race, blue iris,[16] and genetic mutations, whereas modifiable risk factors include smoking,[17,18] systemic arterial hypertension (SAH),[16,19] and diet.[20-23] Smokers have 6 times higher risk of developing dry AMD than nonsmokers.[24]

Genome-wide association studies have identified risk variants in the *ARMS2*, *HTRA1*, and *PLEKHA1* genes on chromosome 10,[25] the *CFH Y402 H*[26] gene on chromosome 1, and the *TIMP3* gene.[25] Genetics and risk scoring that includes age, sex, and smoking

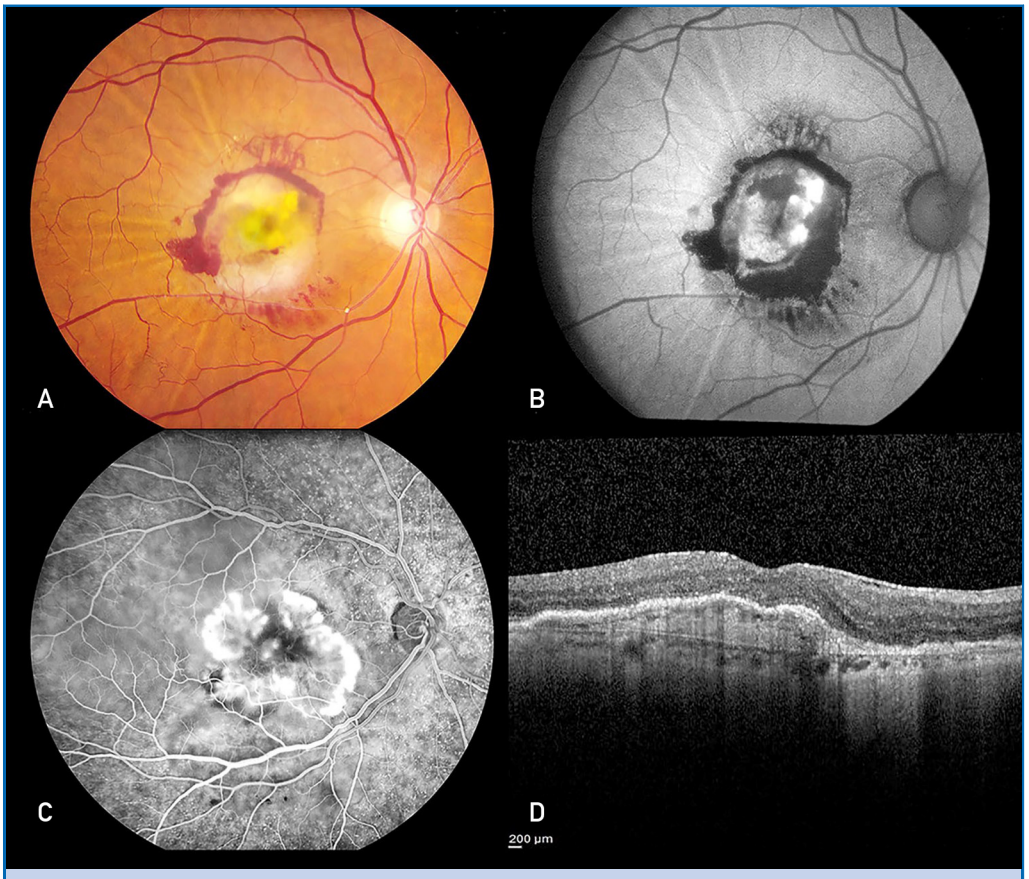

FIGURE 1. Multimodal imaging in neovascular age-related macular degeneration. (A) Color fundus photograph of macular neovascularization (MNV) seen as yellow gray lesion with surrounding hemorrhage. (B) Corresponding fundus autofluorescence showing mixed hyperautofluorescence and hypoautofluorescence. (C) Fluorescein angiography showing leakage from the MNV seen as lacy hyperfluorescence. (D) Optical coherence tomography showing subretinal pigment epithelial hyperreflective lesion suggestive of MNV.

can predict the cumulative risk of developing late AMD,[27] but given the variability in age at disease onset, progression, and clinical manifestations, genetic factors are probably just one of the many contributors to AMD development and further studies are needed to establish direct causality. At this time, neither the American Academy of Ophthalmology nor any of the major retina societies recommend genetic testing for AMD because altering the disease trajectory can only be achieved with the abovementioned lifestyle modifications. A healthy lifestyle with a low-fat diet, control of SAH and lipids, and cessation of smoking is appropriate for AMD risk mitigation just as it for decreasing the risk of cardiovascular disease.

CLINICAL FEATURES AND STAGING

Age-related macular degeneration is usually classified into early and late stages by clinicians, whereas clinical trials frequently use the Age-Related Eye Diseases Study (AREDS) severity scale.[28] In early AMD, vision changes are absent or mild (blurred vision, decreased contrast sensitivity, and impaired dark adaptation), whereas late AMD presents with distortion of images (metamorphopsia), central scotomas, and loss of central vision.

Early AMD

Early AMD is often asymptomatic, but some individuals may notice mild central distortion and difficulty in reading in low light. Drusen,

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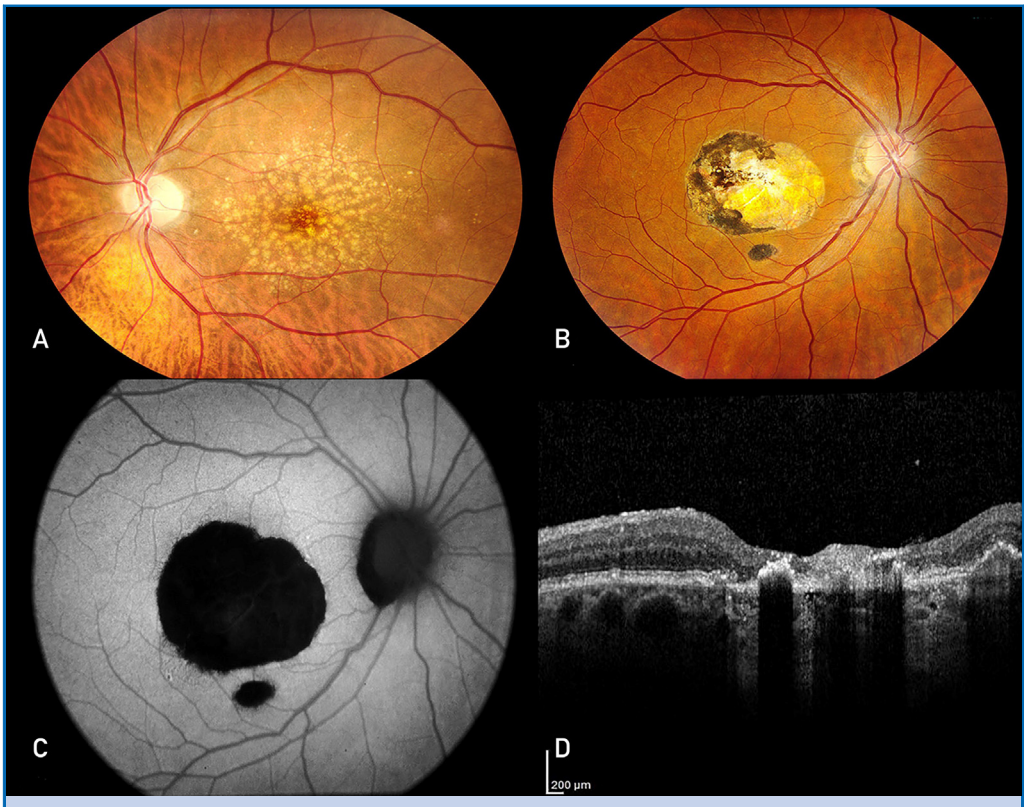

FIGURE 2. Multimodal imaging in dry age-related macular degeneration. (A) Color fundus photograph showing drusen. (B) Color fundus photograph of a patient with geographic atrophy with well demarcated borders. (C)The corresponding area of geographic atrophy on fundus autofluorescence appearing as a decreased autofluorescence. (D) Optical coherence tomography of geographic atrophy seen as loss of outer retinal layers.

small yellowish deposits composed of lipids and proteins that are situated between the RPE and Bruch membrane, are the first visible signs and are the clinical hallmark of AMD. Both the size and number of drusen contribute to the risk of AMD progression. Drusen often progress over time, sometimes followed by more severe forms of AMD and loss of central vision.[29] The AREDS found that specific combinations of vitamins slow progression of drusen to advanced AMD in 25% of patients.[30]

Intermediate AMD

Intermediate AMD is defined as any medium-sized drusen or 1 large drusen and/or GA of the RPE not involving the center of macula that may cause mild metamorphopsia. The 5-year risk of progression from intermediate to advanced AMD is approximately 18%.[31]

Advanced AMD

Neovascular AMD. Neovascular AMD, the most common form of advanced AMD,[32] occurs when new choroidal or retinal blood vessels grow into the sub-RPE and subretinal spaces. The resultant fluid, hemorrhage, lipid exudates, or detachment of the RPE, if untreated, lead to irreversible, severe vision loss and fibrovascular scarring sometimes with outer retinal atrophy.

Geographic Atrophy. Geographic atrophy, the advanced form of dry AMD, is characterized by loss of the RPE, photoreceptors, and choriocapillaris. Progression of atrophy often leads to progressive, permanent loss of central vision, although this loss occurs more slowly than that experienced by patients with nAMD.[33-35] In fact, sudden loss of vision in

a patient with GA should raise the suspicion of newly developed neovascularization and should prompt a referral.

DIAGNOSIS AND IMAGING

Individuals older than 55 years should undergo a dilated fundus examination to screen for macular degeneration. For patients at risk of developing advanced AMD (those with a previous diagnosis of early AMD, a strong family history, and smokers), regular monitoring of vision with an inexpensive, low-tech Amsler grid card is an easy and cost-effective way to identify progression; however, the sensitivity is disappointingly low. For patients with early and intermediate AMD, home monitoring devices can be used (eg, ForeseeHome) but obtaining coverage with insurance can sometimes be challenging.

The gold standard for diagnosing AMD remains a thorough ophthalmologic examination with appropriate ancillary testing. Figures 1 and 2 show the multimodal imaging techniques used in evaluating patients with AMD.

Color fundus photography is a well-established and widely accepted technique for documenting fundus changes and assessing progression by capturing high-resolution images of the retina. Photography is a simple, noninvasive, widely available, cost-effective tool for assessing the macula.[36]

Fundus autofluorescence produces high contrast retinal images by detecting natural fluorescence emitted by endogenous breakdown products from photoreceptor outer segments that accumulate as lipofuscin in the RPE.[37] Autofluorescence has become the gold standard for detecting and measuring GA areas because hypoautofluorescence areas of RPE loss are surrounded by high contrast borders of hyperfluorescence.[38-43]

Fluorescein angiography (FA) includes the intravenous injection of fluorescein dye followed by repeated imaging of the retina (through 10 minutes) with short-wavelength excitation light through barrier filters. Until the recent introduction of optical coherence tomography, FA had been the gold standard for diagnosing MNV.[36]

Indocyanine green angiography better (compared with FA) visualizes the choroidal vessels because the high binding affinity of the dye to plasma proteins enables only minimal dye leakage from the choriocapillaris. The infrared wavelength (795-805 nm peak fluorescence emission) of indocyanine green enables better visualization through overlying pigment, fluid, lipid, and hemorrhage than fluorescein.[44]

Spectral-domain optical coherence tomography has recently become the standard for diagnosing and managing nAMD. Optical coherence tomography uses low-coherence laser light that has been reflected from the tissues to reconstruct 3-dimensional, high-resolution images of retina with axial resolution of 3-6 μm. Optical coherence tomography images many of the findings of early, intermediate, and advanced AMD[45-49] and is particularly useful for visualizing and monitoring the fluid compartments of the retina, thus aiding in planning and monitoring of anti-VEGF treatment.

Optical coherence tomography angiography is a noninvasive technique that images the microvasculature of the retina and choroid by detecting blood flow based on motion contrast derived from movement of blood cells. Neovascular membranes are well visualized, with information regarding size and microvascular anatomy.[50]

MANAGEMENT

Current management of early dry AMD focuses on slowing disease progression. Lifestyle changes including smoking cessation,[51,52] physical activity,[53,54] and the consumption of a Mediterranean diet[55,56] have been shown to slow progression to nAMD. The AREDS1 and AREDS2 trials found that patients with intermediate AMD in both eyes or those with intermediate AMD in 1 eye and advanced AMD in the other eye may benefit from a combination of antioxidants and vitamins.[57] At 5 years, the risk of losing 3 or more lines of visual acuity (VA) reduced by 19%, and the rate of development of advanced AMD reduced by 25%.[57] Higher doses of β-carotene in the AREDS1 formulation increased the risk of developing lung cancer in smokers,[58] so smokers and previous smokers should use the AREDS2 supplements (Table 1), which do not contain β-carotene. The lipid content of drusen suggests that high-dose statin

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TABLE 1. Supplements Used in AREDS2

Supplement	Daily dose
Vitamin C	500 mg
Vitamin E	180 mg
Lutein	10 mg
Zeaxanthin	2 mg
Zinc oxide	80 mg
Cupric oxide	2 mg

Abbreviation: AREDS, age-related eye disease study.

therapy might lead to drusen regression,[59,60] but more research is needed.

Neovascular AMD

Thermal laser ablation and photodynamic therapy were the only available treatments of nAMD in the 1990s and early 2000s, respectively, but poor visual results coupled with the introduction of anti-VEGF therapy have minimized their use except in some cases of polypoidal vasculopathy (a subgroup of type 1 MNV).[61-63]

Vascular endothelial growth factor plays a pivotal role in the development of MNV, so preventing its actions has become the primary treatment of eyes with nAMD.[64] Anti-VEGF drugs are injected into the vitreous via quick, in-office procedures (Figure 3), with low associated risks, few adverse effects, and quick recovery times. Most drugs are packaged in prefilled syringes (that generally become available 1 year after the drug has been approved) with 30- or 32-gauge needles and are injected 3 to 4 mm behind the limbus through the eye's pars plana region. Topical anesthesia usually provides sufficient comfort though some patients require subconjunctival injections of lidocaine. Topical 5% or 10% povidone-iodine reduces the risk of postinjection endophthalmitis but some sensitive patients will have persistent antiseptic—induced surface irritation for 24-48 h after instillation.[65]

FIGURE 3. In-office intravitreal injection technique.

Pegaptanib sodium (Macugen) was the first US Food and Drug Administration (FDA)-approved anti-VEGF drug for the intravitreal treatment of nAMD (2004) but it was quickly replaced by more potent pan—VEGF-A—binding drugs that produce better disease control and superior vision outcomes.[66]

For patients with newly diagnosed nAMD, clinicians have several pharmacologic agents and treatment strategies to choose. Preferred practice patterns for patients with nAMD have increasingly focused on a personalized approach for each patient. Treatment begins with monthly intravitreal anti-VEGF injections until the eye is stable (generally a dry macula and optimal improvement in VA). Most physicians then adopt a treat-and-extend regimen that features injections at each clinic visit, but the time between visits is extended by 2- to 4-week adjustments until the maximum effective interval is determined.[67] Most physicians extend the intervals to a maximum of 12 or 16 weeks (if possible) and then continue injecting at this interval to maintain disease control. The treat-and-extend regimen not only minimizes the numbers of both injections and clinic visits but also achieves improvements in VA that rival those from the phase III registration trials.[68,69] Patients are monitored frequently to look for disease recurrence and minimize the risk of irreversible scarring. Optical coherence tomography imaging is an essential monitoring tool to assess disease status and institute changes in therapy when appropriate.

Anti-VEGF therapy is the standard of care for all subtypes of nAMD, but not all eyes respond adequately, and a decrease in VA is common after years of treatment.[70,71] Drug tolerance/tachyphylaxis may occur in a subset of patients with anti-VEGF refractory and these eyes may benefit from switching medications. Close monitoring of the fellow eye is crucial because the risk of bilateral advanced AMD is high, with almost half of patients

TABLE 2. Currently Available US Food and Drug Administration-Approved Intravitreal Drugs for AMD

Disease	Drug	Biological forms	Target	Dose (mg/mL)
Neovascular AMD	Pegaptanib sodium (Macugen)	Pegylated synthetic RNA-based oligonucleotide	VEGF-A isoform 165	0.3/0.05
	Bevacizumab (Avastin)	Recombinant humanized monoclonal IgG1	VEGF-A all isoforms	1.25/0.05
	Ranibizumab (Lucentis)	Humanized IgG1 antibody fragment	VEGF-A all isoforms	0.5/0.05
	Aflibercept (Eylea)	VEGF-trap	VEGF-A, VEGF-B, PGF, pan-inhibition VEGF	2/0.05
	Brolucizumab (Beovu)	Humanized single-chain antibody fragment	VEGF-A (VEGF110, 121 and 165) and VEGFR-1 and VEGFR-2	6/0.05
Geographic atrophy	Pegcetacoplan (Syfovre)	Synthetic peptide	Complement factor C3	15/0.1
	Avacincaptad pegol (Izervay)	Pegylated RNA aptamer	Complement factor C5	2/0.1

Abbreviations: AMD, age-related macular degeneration; IgG, immunoglobulin G; PGF, placental growth factor; RNA, ribonucleic acid; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

requiring treatment in both eyes within 3 years.[72,73] Long-term follow-up studies show that gains made with the first 2 years of treatment are often not maintained over additional years of follow-up,[74] with atrophy and fibrosis being important causes of late vision loss.[75]

Intravitreal injections are generally safe but associated risks include elevated intraocular pressure, subconjunctival hemorrhage, vitreous hemorrhage, retinal detachment, and endophthalmitis. Endophthalmitis is the most significant vision-threatening complication with reported incidences of 0.019%-0.07%.[76-78] Anti-VEGF drugs leave the eye without being metabolized and enter the systemic circulation where they might increase the risks of SAH, myocardial infarction, cardiac arrest, and stroke (known complications of systemic anti-VEGF therapy), but a recent pooled data analysis of 80,000 patients found that there is no increased risk of acute myocardial infarction, cerebral vascular disease, or major bleeding after administration of bevacizumab, ranibizumab, or aflibercept.[79] Despite 2 decades of intravitreal anti-VEGF injections that now number over 7 million per year, we are still unable to quantify the systemic risks associated with intravitreal therapy.

Our inability to predict a patient's response to therapy, trauma caused by repeated intraocular injections, and the development of retinal atrophy after long-term therapy renders current intravitreal therapeutic regimens suboptimal. The increasing financial and social burdens that intravitreal anti-VEGF therapy imposes on elderly patients and the health care system are challenging, so longer lasting drugs or sustained release formulations of currently available agents would mitigate these. Newer treatments are focused on extending the duration of clinical action to decrease treatment burden and improve adherence, and some investigational drugs aim to increase peak efficacy by targeting non-VEGF biochemical pathways. Angiopoietin-2 blocking drugs have been studied but no advantage over anti-VEGF monotherapy has yet been reported.

Dry AMD

Current management of dry AMD consists of lifestyle modifications, timely recognition of early MNV, intravitreal pharmacotherapy, and low vision aids. Nutritional supplementation to reduce the oxidative damage caused by smoking, ultraviolet light exposure, and oxidative stress should be prescribed to patients with intermediate AMD,[80] but current nutritional supplements only decrease the chances of progression to nAMD. Antioxidant drugs, complement cascade inhibitors, visual cycle inhibitors, gene therapy, cell-based therapy, and neuroprotective agents are in clinical trials, but few have shown encouraging results.

Two intravitreal inhibitors of the complement cascade have recently received the US FDA approval for the treatment of GA. Pegcetacoplan (Syfovre), a complement 3 inhibitor given monthly or every other month, reduced the growth rate of GA by 20%-29%,[81] and avacincaptad pegol (Izervay), an anti-C5 aptamer, reduced GA growth by 27.3%-27.8%,[82] but neither drug prevented a decline in vision function compared with the sham group over the course of 2 years. The retina community remains divided over the value

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of these drugs, so their use in the United States has been limited. Table 2 summarizes the currently available US FDA-approved intravitreal drugs for AMD.

LOW VISION

Despite receiving appropriate prophylaxis and timely treatment of advanced disease, many patients will experience significant vision loss. Patients with early AMD, therefore, should be educated about the progressive nature of the disease and the likelihood of vision decline. When patients develop irreversible vision loss, a common-sense approach to life with the thoughtful imposition of limitations becomes important to prevent injuries, but patients should also be encouraged to make the best use of the vision they have to perform daily activities. Vision rehabilitation with low vision aids and occupational training should be provided to improve the patient's function.[83] Patients with decreased vision should undergo a comprehensive low vision evaluation with appropriate adjustments in the manifest refraction, demonstration and testing of optical (magnification) devices, and optimization of their environments. Commonly used low vision aids include magnifiers, high-power reading glasses, telescope-mounted glasses, and closed-circuit television. At home monitoring of vision with an Amsler grid or FDA-approved home monitoring tool to detect reactivation of or progression to nAMD should be encouraged.

The Implantable Miniature Telescope, an FDA-approved, cost-effective lens system, may be effective for motivated patients with bilateral, late AMD who undergo cataract operation.[84,85] This magnifies objects by 2.2× in the surgical eye (although it reduces the width of the visual field) and enables patients to better see fine detail; the other eye receives a standard implant to provide wide-field ambulatory vision. In addition to low vision aids, newly invented assistive technology includes wearable electronic vision enhancement systems, which provide hands free magnification that enhance images, and improvement VA and contrast sensitivity. Irisvision, OrCam, eSight, Vision Buddy, and Acesight are wearable devices that contribute to vision rehabilitation in patients with central vision loss. Clinical depression may be exacerbated by the vision effects of AMD, so primary care physicians should enquire about depression symptoms and initiate timely referrals to the appropriate providers.[86]

CONCLUSION

Age-related macular degeneration is a global health problem that significantly decreases patients' ability to read, drive, and identify faces and adversely impacts their quality of life. The use of specially formulated multivitamins (zinc, copper, vitamin C, vitamin E, lutein, and zeaxanthin) limits the development of nAMD in patients with intermediate AMD. Multimodal imaging categorizes disease severity and identifies patients who are candidates for pharmacologic therapy. The widespread use of anti-VEGF therapy for nAMD has transformed visual outcomes and reduced the incidence of blindness by 50%. Therapies for GA have been developed and approved but there is limited evidence regarding their ability to preserve vision. In summary, preserving vision in patients with advanced AMD remains an unmet need and continued research is required.

FUTURE PERSPECTIVES

Current research needs include the development of treatments to prevent vision loss from macular atrophy. Several companies are developing sustained delivery anti-VEGF drugs and devices to reduce treatment burden and limit fibrosis.[87] Once central vision has been lost owing to RPE and photoreceptor cell death, regenerative strategies such as RPE graft transplantation, stem cell-derived graft transplants, optogenetics, and bionic eye prosthetic devices will be needed.

POTENTIAL COMPETING INTERESTS

Dr Stewart is the Professor of Ophthalmology Research of Knights Templar Eye Foundation, consultant for Alkahest, Bayer, Biogen, Revana, reports research support from Alexion, and leadership role as IJCAHPO President. Dr Miller reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from the University of Florida Ophthalmology Grand Rounds, leadership role in the Legislative Chair, Florida Society of Ophthalmology and YO Advocacy Subcommittee Chair,

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Abbreviations and Acronyms: **AMD,** age-related macular degeneration; **AREDS,** Age-Related Eye Diseases Study; **FA,** fluorescein angiography; **FDA,** Food and Drug Administration; **GA,** geographic atrophy; **MNV,** macular neovascularization; **nAMD,** neovascular age-related macular degeneration; **RPE,** retinal pigment epithelium; **SAH,** systemic arterial hypertension; **VEGF,** vascular endothelial growth factor; **VA,** visual acuity

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REFERENCES

1. Bourne RRA, Jonas JB, Bron AM, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol*. 2018;102(5):575-585. https://doi.org/10.1136/bjophthalmol-2017-311258.
2. Brody BL, Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology*. 2001;108(10):1893-1900. https://doi.org/10.1016/s0161-6420(01)00754-0; discussion 1900-1901.
3. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106-e116. https://doi.org/10.1016/S2214-109X(13)70145-1.
4. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140(12):1202-1208. https://doi.org/10.1001/jamaophthalmol.2022.4401.
5. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci*. 1995;36(1):182-191.
6. Klein R, Klein BEK, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology*. 2006;113(3):373-380. https://doi.org/10.1016/j.ophtha.2005.12.013.
7. Ferris FL, III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640-1642. https://doi.org/10.1001/archopht.1984.01040031330019.
8. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. *Neuron*. 2012;75(1):26-39. https://doi.org/10.1016/j.neuron.2012.06.018.
9. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group. *Arch Ophthalmol*. 1997;115(6):741-747. https://doi.org/10.1001/archopht.1997.01100150743009.
10. Country MW. Retinal metabolism: a comparative look at energetics in the retina. *Brain Res*. 2017;1672:50-57. https://doi.org/10.1016/j.brainres.2017.07.025.
11. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. *J Pathol*. 2014;232(2):151-164. https://doi.org/10.1002/path.4266.
12. Xu H, Chen M. Targeting the complement system for the management of retinal inflammatory and degenerative diseases. *Eur J Pharmacol*. 2016;787:94-104. https://doi.org/10.1016/j.ejphar.2016.03.001.
13. Park YG, Park YS, Kim IB. Complement system and potential therapeutics in age-related macular degeneration. *Int J Mol Sci*. 2021;22(13):6851. https://doi.org/10.3390/ijms22136851.
14. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology*. 2012;119(3):571-580. https://doi.org/10.1016/j.ophtha.2011.09.027.
15. Rudnicka AR, Kapetanakis VV, Jarrar Z, et al. Incidence of late-stage age-related macular degeneration in American Whites: systematic review and meta-analysis. *Am J Ophthalmol*. 2015;160(1):85-93.e3. https://doi.org/10.1016/j.ajo.2015.04.003.
16. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol*. 2010;10:31. https://doi.org/10.1186/1471-2415-10-31.
17. Houston T. Smoking and age-related macular degeneration. *Am Fam Phys*. 2001;63(2):225.
18. Nidhi B, Mamatha BS, Padmaprabhu CA, Pallavi P, Vallikannan B. Dietary and lifestyle risk factors associated with age-related macular degeneration: a hospital based study. *Indian J Ophthalmol*. 2013;61(12):722-727. https://doi.org/10.4103/0301-4738.120218.
19. Choudhury F, Varma R, McKean-Cowdin R, Klein R, Azen SP; Los Angeles Latino Eye Study Group. Risk factors for four-year incidence and progression of age-related macular degeneration: the los angeles latino eye study. *Am J Ophthalmol*. 2011;152(3):385-395. https://doi.org/10.1016/j.ajo.2011.02.025.
20. Ristau T, Ersoy L, Hahn M, et al. Nongenetic risk factors for neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2014;55(8):5228-5232. https://doi.org/10.1167/iovs.14-14299.
21. Hyman L, Neborsky R. Risk factors for age-related macular degeneration: an update. *Curr Opin Ophthalmol*. 2002;13(3):171-175. https://doi.org/10.1097/00055735-200206000-00007.
22. Velilla S, García-Medina JJ, García-Layana A, et al. Smoking and age-related macular degeneration: review and update. *J Ophthalmol*. 2013;2013:895147. https://doi.org/10.1155/2013/895147.
23. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol*. 2000;118(3):351-358. https://doi.org/10.1001/archopht.118.3.351.
24. Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology*. 2004;111(7):1280-1287. https://doi.org/10.1016/j.ophtha.2003.11.010.
25. Fritsche LG, Igl W, Bailey JNC, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134-143. https://doi.org/10.1038/ng.3448.
26. Schaumberg DA, Hankinson SE, Guo Q, Rimm E, Hunter DJ. A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk

factors. *Arch Ophthalmol*. 2007;125(1):55-62. https://doi.org/10.1001/archopht.125.1.55.

27. Buitendijk GHS, Rochtchina E, Myers C, et al. Prediction of age-related macular degeneration in the general population: the Three Continent AMD Consortium. *Ophthalmology*. 2013;120(12):2644-2655. https://doi.org/10.1016/j.ophtha.2013.07.053.
28. Liew G, Joachim N, Mitchell P, Burlutsky G, Wang JJ. Validating the AREDS simplified severity scale of age-related macular degeneration with 5- and 10-year incident data in a population-based sample. *Ophthalmology*. 2016;123(9):1874-1878. https://doi.org/10.1016/j.ophtha.2016.05.043.
29. Abdelsalam A, Del Priore L, Zarbin MA. Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression. *Surv Ophthalmol*. 1999;44(1):1-29. https://doi.org/10.1016/s0039-6257(99)00072-7.
30. Davis MD, Gangnon RE, Lee L-Y, et al. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS report no. 17. *Arch Ophthalmol*. 2005;123(11):1484-1498. https://doi.org/10.1001/archopht.123.11.1484.
31. Tikellis G, Robman LD, Dimitrov P, Nicolas C, McCarty CA, Guymer RH. Characteristics of progression of early age-related macular degeneration: the cardiovascular health and age-related maculopathy study. *Eye (Lond)*. 2007;21(2):169-176. https://doi.org/10.1038/sj.eye.6702151.
32. Klein R, Klein BEK, Tomany SC, Meuer SM, Huang G-H. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology*. 2002;109(10):1767-1779. https://doi.org/10.1016/s0161-6420(02)01146-6.
33. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009;127(9):1168-1174. https://doi.org/10.1001/archophthalmol.2009.198.
34. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the age-related eye disease study report number 6. *Am J Ophthalmol*. 2001;132(5):668-681. https://doi.org/10.1016/s0002-9394(01)01218-1.
35. Joachim N, Mitchell P, Kifley A, Rochtchina E, Hong T, Wang JJ. Incidence and progression of geographic atrophy: observations from a population-based cohort. *Ophthalmology*. 2013;120(10):2042-2050. https://doi.org/10.1016/j.ophtha.2013.03.029.
36. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology*. 1999;106(9):1768-1779. https://doi.org/10.1016/S0161-6420(99)90340-8.
37. Ach T, Huisingh C, McGwin G, et al. Quantitative autofluorescence and cell density maps of the human retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. 2014;55(8):4832-4841. https://doi.org/10.1167/iovs.14-14802.
38. Schmitz-Valckenberg S, Brinkmann CK, Alten F, et al. Semiautomated image processing method for identification and quantification of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(10):7640-7646. https://doi.org/10.1167/iovs.11-7457.
39. McBain VA, Townend J, Lois N. Fundus autofluorescence in exudative age-related macular degeneration. *Br J Ophthalmol*. 2007;91(4):491-496. https://doi.org/10.1136/bjo.2006.095109.
40. Kellner U, Kellner S, Weinitz S. Fundus autofluorescence (488 NM) and near-infrared autofluorescence (787 NM) visualize different retinal pigment epithelium alterations in patients with age-related macular degeneration. *Retina*. 2010;30(1):6-15. https://doi.org/10.1097/iae.0b013e3181b8348b.
41. Vujosevic S, Vaclavik V, Bird AC, Leung I, Dandekar S, Peto T. Combined grading for choroidal neovascularisation: colour, fluorescein angiography and autofluorescence images. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(10):1453-1460. https://doi.org/10.1007/s00417-007-0574-9.
42. Framme C, Bunse A, Sofroni R, et al. Fundus autofluorescence before and after photodynamic therapy for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmic Surg Lasers Imaging*. 2006;37(5):406-414. https://doi.org/10.3928/15428877-20060901-08.
43. Peng Q, Dong Y, Zhao PQ. Fundus autofluorescence in exudative age-related macular degeneration. *Genet Mol Res*. 2013;12(4):6140-6148. https://doi.org/10.4238/2013.December.2.11.
44. Desmettre T, Devoisselle JM, Mordon S. Fluorescence properties and metabolic features of indocyanine green (ICG) as related to angiography. *Surv Ophthalmol*. 2000;45(1):15-27. https://doi.org/10.1016/s0039-6257(00)00123-5.
45. Yang S, Gao Z, Qiu H, et al. Low-reflectivity drusen with overlying RPE damage revealed by spectral-domain OCT: hint for the development of age-related macular Degeneration. *Front Med (Lausanne)*. 2021;8:706502. https://doi.org/10.3389/fmed.2021.706502.
46. Veerappan M, El-Hage-Sleiman AM, Tai V, et al. Optical coherence tomography reflective drusen substructures predict progression to geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2016;123(12):2554-2570. https://doi.org/10.1016/j.ophtha.2016.08.047.
47. Ouyang Y, Heussen FM, Hariri A, Keane PA, Sadda SR. Optical coherence tomography-based observation of the natural history of drusenoid lesion in eyes with dry age-related macular degeneration. *Ophthalmology*. 2013;120(12):2656-2665. https://doi.org/10.1016/j.ophtha.2013.05.029.
48. Balaratnasingam C, Cherepanoff S, Dolz-Marco R, et al. Cuticular drusen: clinical phenotypes and natural history defined using multimodal imaging. *Ophthalmology*. 2018;125(1):100-118. https://doi.org/10.1016/j.ophtha.2017.08.033.
49. Wu Z, Fletcher EL, Kumar H, Greferath U, Guymer RH. Reticular pseudodrusen: a critical phenotype in age-related macular degeneration. *Prog Retin Eye Res*. 2022;88:101017. https://doi.org/10.1016/j.preteyeres.2021.101017.
50. Choi W, Moult EM, Waheed NK, et al. Ultrahigh-speed, swept-source optical coherence tomography angiography in nonexudative age-related macular degeneration with geographic atrophy. *Ophthalmology*. 2015;122(12):2532-2544. https://doi.org/10.1016/j.ophtha.2015.08.029.
51. Cong R, Zhou B, Sun Q, Gu H, Tang N, Wang B. Smoking and the risk of age-related macular degeneration: a meta-analysis. *Ann Epidemiol*. 2008;18(8):647-656. https://doi.org/10.1016/j.annepidem.2008.04.002.
52. Carneiro Â, Andrade JP. Nutritional and lifestyle interventions for age-related macular degeneration: a review. *Oxid Med Cell Longev*. 2017;2017:6469138. https://doi.org/10.1155/2017/6469138.
53. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. *Arch Ophthalmol*. 2003;121(6):785-792. https://doi.org/10.1001/archopht.121.6.785.
54. Liu L, Majithia S, Tham Y-C. Physical activity and age-related macular degeneration: a systematic literature review and meta-analysis. *Am J Ophthalmol*. 2018;185:123. https://doi.org/10.1016/j.ajo.2017.10.013.
55. Hogg RE, Woodside JV, McGrath A, et al. Mediterranean diet score and its association with age-related macular degeneration: the European Eye Study. *Ophthalmology*. 2017;124(1):82-89. https://doi.org/10.1016/j.ophtha.2016.09.019.
56. Keenan TD, Agrón E, Mares J, et al. Adherence to the Mediterranean diet and progression to late age-related macular degeneration in the Age-Related Eye Disease Studies 1 and 2. *Ophthalmology*. 2020;127(11):1515-1528. https://doi.org/10.1016/j.ophtha.2020.04.030.
57. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose

supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417-1436. https://doi.org/10.1001/archopht.119.10.1417.

58. Heinonen OP, Huttunen JK, Albanes D, et al. Effect of vitamin-E and beta-carotene on the incidence of lung-cancer and other cancers in male smokers. *N Engl J Med*. 1994;330(15):1029-1035. https://doi.org/10.1056/NEJM199404143301501.
59. Guymer RH, Baird PN, Varsamidis M, et al. Proof of concept, randomized, placebo-controlled study of the effect of simvastatin on the course of age-related macular degeneration. *PLOS ONE*. 2013;8(12):e83759. https://doi.org/10.1371/journal.pone.0083759.
60. Miller JW. Beyond VEGF—the Weisenfeld lecture. *Invest Ophthalmol Vis Sci*. 2016;57(15):6911-6918. https://doi.org/10.1167/iovs.16-21201.
61. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration—reply. *N Engl J Med*. 2008;359(16):1736-1738.
62. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. *Arch Ophthalmol*. 1999;117(10):1329-1345.
63. Bressler NM. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—tap report 2. *Arch Ophthalmol*. 2001;119(2):198-207.
64. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. *Drugs*. 2008;68(8):1029-1036. https://doi.org/10.2165/00003495-200868080-00002.
65. Lau PET, Jenkins KS, Layton CJ. Current evidence for the prevention of endophthalmitis in anti-VEGF intravitreal injections. *J Ophthalmol*. 2018;2018:8567912. https://doi.org/10.1155/2018/8567912.
66. Ahmadi MA, Lim JI. Pharmacotherapy of age-related macular degeneration. *Expert Opin Pharmacother*. 2008;9(17):3045-3052. https://doi.org/10.1517/14656560802473480.
67. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*. 2015;122(1):146-152. https://doi.org/10.1016/j.ophtha.2014.07.041.
68. Chin-Yee D, Eck T, Fowler S, Hardi A, Apte RS. A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration. *Br J Ophthalmol*. 2016;100(7):914-917. https://doi.org/10.1136/bjophthalmol-2015-306987.
69. Fong KCS, Kirkpatrick N, Mohamed Q, Johnston RL. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration using a variable frequency regimen in eyes with no previous treatment. *Clin Exp Ophthalmol*. 2008;36(8):748-755. https://doi.org/10.1111/j.1442-9071.2008.01873.x.
70. Broadhead GK, Hong T, Chang AA. Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration. *Acta Ophthalmol*. 2014;92(8):713-723. https://doi.org/10.1111/aos.12463.
71. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Dev Ther*. 2016;10:1857-1867. https://doi.org/10.2147/DDDT.S97653.
72. Zarranz-Ventura J, Liew G, Johnston RL, et al. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology*. 2014;121(10):1966-1975. https://doi.org/10.1016/j.ophtha.2014.04.026.
73. Silva R, Cachulo ML, Fonseca P, et al. Age-related macular degeneration and risk factors for the development of choroidal neovascularisation in the fellow eye: a 3-year follow-up study. *Ophthalmologica*. 2011;226(3):110-118. https://doi.org/10.1159/000329473.
74. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751-1761. https://doi.org/10.1016/j.ophtha.2016.03.045.
75. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2019;126(2):252-260. https://doi.org/10.1016/j.ophtha.2018.08.035.
76. Pancholy M, Storey PP, Levin HJ, et al. Endophthalmitis following intravitreal anti-vascular endothelial growth factor therapy: changes in incidence and outcomes over a 9-year period. *Curr Eye Res*. 2021;46(9):1370-1377. https://doi.org/10.1080/02713683.2021.1874023.
77. Morioka M, Takamura Y, Nagai K, et al. Incidence of endophthalmitis after intravitreal injection of an anti-VEGF agent with or without topical antibiotics. *Sci Rep*. 2020;10(1):22122. https://doi.org/10.1038/s41598-020-79377-w.
78. Shrestha R, Karki P, Joshi SN. Outcome of intravitreal bevacizumab injection without pre and postoperative antibiotics. *BMC Ophthalmol*. 2020;20(1):145. https://doi.org/10.1186/s12886-020-01420-1.
79. Maloney MH, Payne SR, Herrin J, Sangaralingham LR, Shah ND, Barkmeier AJ. Risk of systemic adverse events after intravitreal bevacizumab, ranibizumab, and aflibercept in routine clinical practice. *Ophthalmology*. 2021;128(3):417-424. https://doi.org/10.1016/j.ophtha.2020.07.062.
80. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the age-related eye disease study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005-2015. https://doi.org/10.1001/jama.2013.4997.
81. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186-195. https://doi.org/10.1016/j.ophtha.2019.07.011.
82. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128(4):576-586. https://doi.org/10.1016/j.ophtha.2020.08.027.
83. Stelmack JA, Tang XC, Reda DJ, et al. Outcomes of the veterans affairs low vision intervention trial (LOVIT). *Arch Ophthalmol*. 2008;126(5):608-617. https://doi.org/10.1001/archopht.126.5.608.
84. Hudson HL, Lane SS, Heier JS, et al. Implantable miniature telescope for the treatment of visual acuity loss resulting from end-stage age-related macular degeneration: 1-year results. *Ophthalmology*. 2006;113(11):1987-2001. https://doi.org/10.1016/j.ophtha.2006.07.010.
85. Brown GC, Brown MM, Lieske HB, Lieske PA, Brown KS, Lane SS. Comparative effectiveness and cost-effectiveness of the implantable miniature telescope. *Ophthalmology*. 2011;118(9):1834-1843. https://doi.org/10.1016/j.ophtha.2011.02.012.
86. Rovner BW, Casten RJ, Tasman WS. Effect of depression on vision function in age-related macular degeneration. *Arch Ophthalmol*. 2002;120(8):1041-1044. https://doi.org/10.1001/archopht.120.8.1041.
87. Ammar MJ, Hsu J, Chiang A, Ho AC, Regillo CD. Age-related macular degeneration therapy: a review. *Curr Opin Ophthalmol*. 2020;31(3):215-221. https://doi.org/10.1097/ICU.0000000000000657.