Chapter 115: Age-Related Macular Degeneration

Alisa K. Escano; Casey S. Washington

KEY CONCEPTS

KEY CONCEPTS

1. The hallmark sign of age-related macular degeneration (AMD) is the development of drusen in the macula. Drusen are yellow deposits of lipids between the retinal pigment epithelial and Bruch's membrane that can develop with age.
2. AMD is identified as the leading cause of blindness in the industrialized world and a top cause of blindness worldwide.
3. The two most important risk factors for AMD are age and smoking.
4. The goal of treatment is to slow progression of AMD and prevent severe visual impairment or blindness.
5. Smoking cessation is the main modifiable risk factor that will slow progression of AMD. Pharmacists and other health professionals can play a vital role in helping people stop smoking.
6. Antioxidant vitamins and minerals may prevent cellular damage in the retina caused by the formation of free radicals through light absorption. Use may benefit patients the most with medium- or large-sized drusen and/or geographic atrophy in at least one eye.
7. For most patients with wet AMD and choroidal neovascularization, the use of intravitreal vascular endothelial growth factor (VEGF) inhibitors and other inhibitor-like drugs have led to improvement in visual acuity.
8. The appeal of the ranibizumab treat and extend (TREX) approach is the reduction of office visits and medication cost.
9. VEGF inhibitors and antioxidant vitamins and minerals are the only pharmacologic therapies available that have been shown to improve and stabilize visual acuity in patients with intermediate to advanced AMD.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the first three age-related macular degeneration videos from the National Eye Institute at https://youtube.com/playlist?list=PLNol8zIT_P1Bjl8o7HNMCybk1tA3s0SlN. These short videos totaling 3 minutes provide a brief overview to age-related macular degeneration and animation of the pathophysiology. These videos are useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

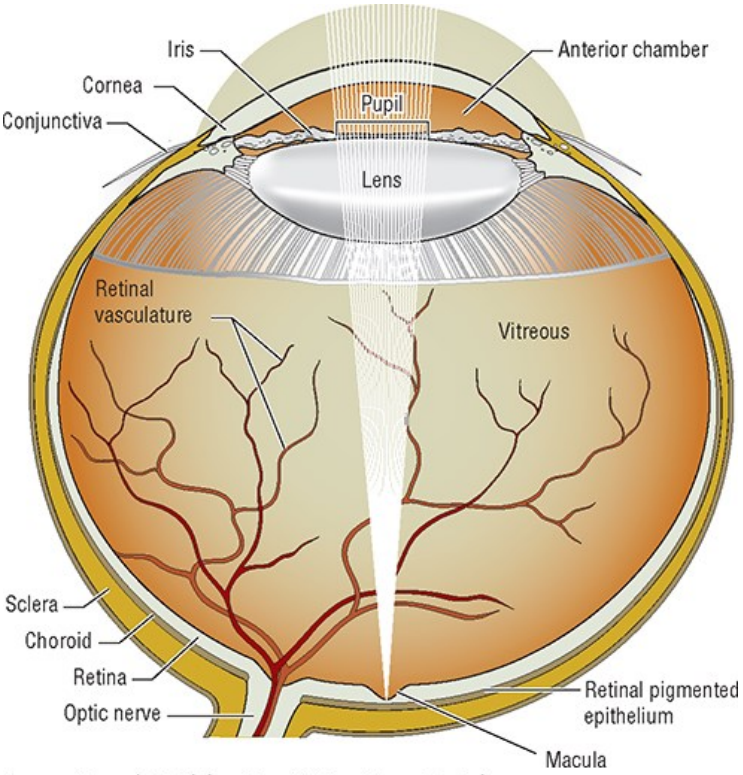
INTRODUCTION

Age-related macular degeneration (AMD) is a neurodegenerative disease that produces irreversible loss of central vision due to damage to the macula, the center region of the retina. AMD is a leading cause of blindness due to age-related changes in the macula and, specifically, the photoreceptor–retinal pigment epithelial (RPE) complex.[2]

A general familiarity with the anatomy of the eye including the macula and photoreceptor–RPE complex will aid in understanding the disease and treatment mechanisms (Figs. 115-1 and 115-2).[3,4] The macula in the middle of the retina is responsible for all central vision, a significant part of color vision, and the fine detail images. The photoreceptor cells of the macula identify light and then transfer the information to the brain to produce an image. Central vision is needed to read, write, drive, watch television, and other typical activities of daily living. AMD reduces central vision, visual acuity, and blue-yellow color sensitivity leading to significant disability (Fig. 115-3).[5]

FIGURE 115-1

Anatomy of the eye. The macula, in the center of the retina, is responsible for central vision, color vision, and fine details.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

FIGURE 115-2

Detailed anatomy of the photoreceptor–RPE complex. The photoreceptor–RPE complex in the normal state and in a state with AMD that shows the breakdown of the RPE with drusen formation and apoptosis of photoreceptors contributing to the loss of vision with AMD. *(Reproduced, with permission, from Chichagova V, Hallam D, Collin J, Zerti D, Dorgau B, Felemban M, Lako M, Steel DH. Cellular regeneration strategies for macular degeneration: past, present and future. Eye (Lond). 2018 May;32(5):946-971.)*

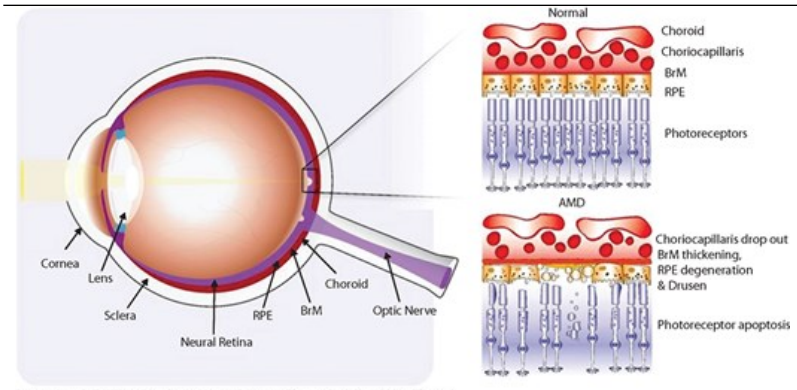


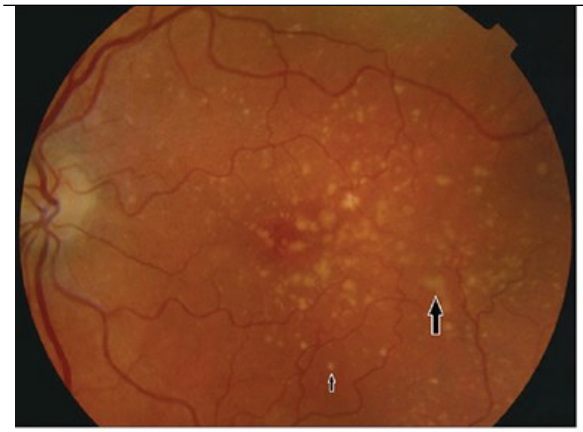
FIGURE 115-3

Effects of the loss of central vision with AMD. *(From National Eye Institute, National Institutes of Health, Washington, DC.)*

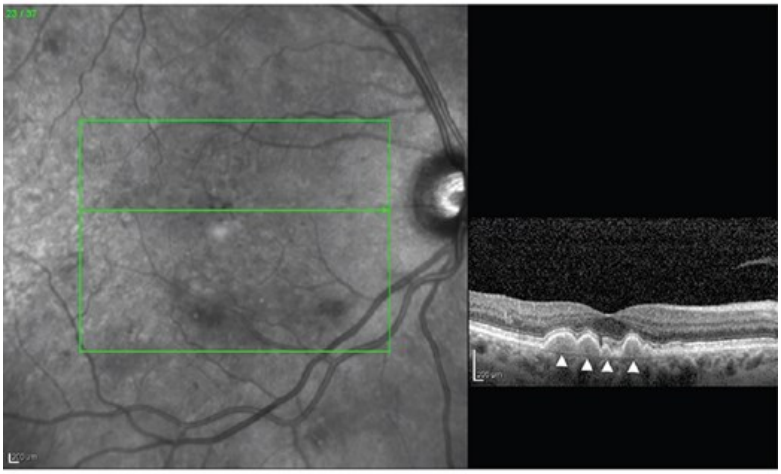
1 The hallmark sign of AMD is the development of drusen in the macula. Drusen are yellow deposits of lipids between the RPE and Bruch's membrane that can develop with age (Fig. 115-4). Bruch's membrane is an extracellular layer separating the RPE from choroidal capillaries in the eye. Small drusen without additional abnormalities have a lower risk of progression to severe disease than large drusen.

FIGURE 115-4

Age-related macular degeneration (AMD). (*A*) Discrete (**small arrow**) and large confluent (**large arrow**) drusen. (*B*) Optical coherence tomography scan of large confluent drusen (**arrowheads**). *(Reproduced, with permission, from Riordan-Eva P, Augsburger JJ, eds. Vaughan & Asbury's General Ophthalmology. 19th ed. New York: McGraw Hill; 2018.)*



A



B

Two distinct types of AMD have been identified: geographic atrophy (GA) "dry" and choroidal neovascularization (CNV), exudative "wet" (Fig. 115-5). Disease progression is unpredictable as visual disturbances do not correlate with drusen formation. Patients can monitor visual changes with an Amsler grid by using one eye at a time and looking for any distortions in the grid (Fig. 115-6).

FIGURE 115-5

Age-related macular degeneration consisting of scattered yellow drusen in the macula (dry form) and a crescent of fresh hemorrhage temporal to the fovea from a subretinal neovascular membrane (wet form). *(Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2019.)*

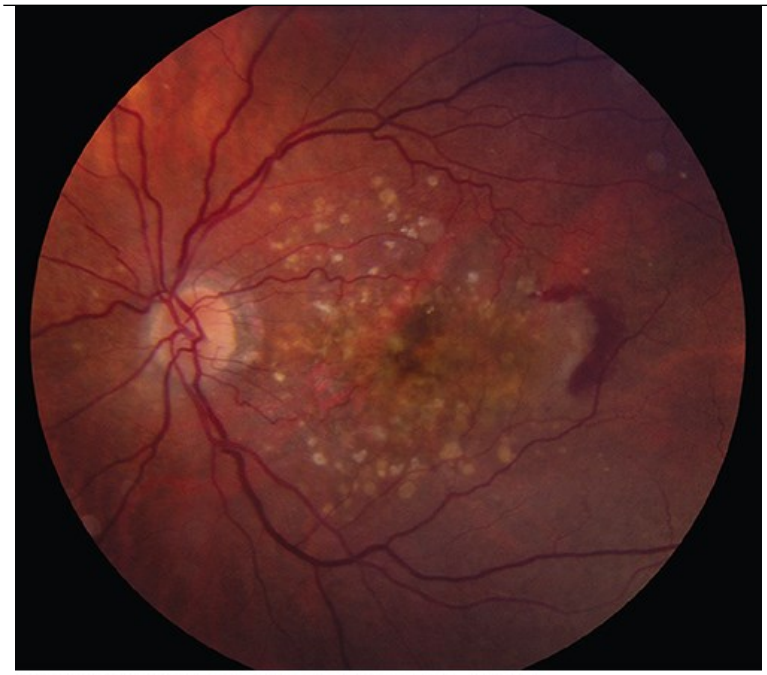
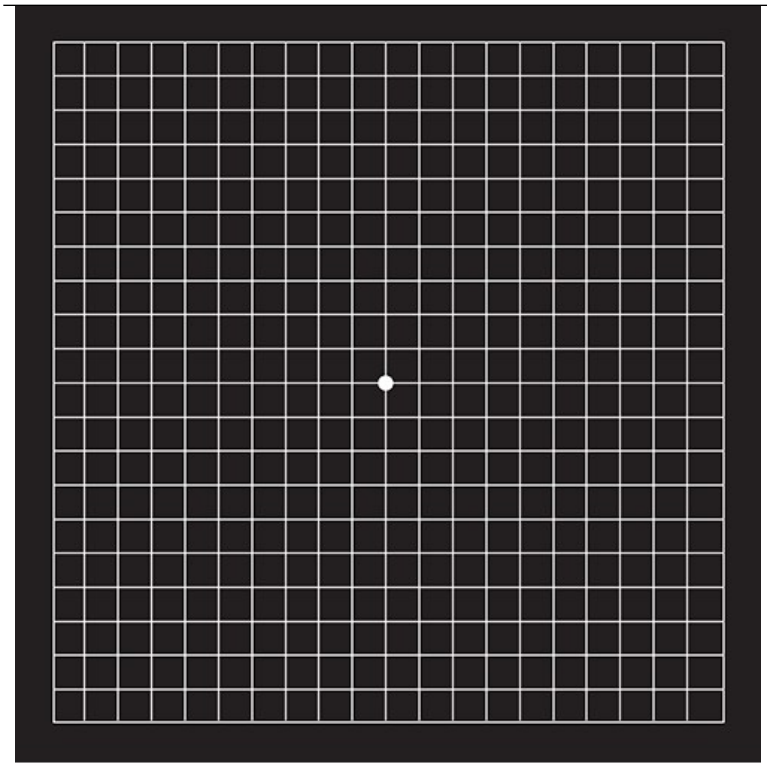


FIGURE 115-6

Amsler grid for monitoring vision by tracking any distortions in the grid lines while focusing on the center dot. *(Reproduced, with permission, from Riordan-Eva P, Augsburger JJ, eds. Vaughan & Asbury's General Ophthalmology. 19th ed. New York: McGraw Hill; 2018.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The American Academy of Ophthalmology defines AMD by the presence of one of the following criteria[1]:

- Presence of at least intermediate-size drusen (63 µm or larger in diameter)
- RPE abnormalities (hypopigmentation or hyperpigmentation)
- Reticular pseudodrusen
- Presence of any of the following features: RPE GA, CNV, polypoidal choroidal vasculopathy, retinal angiomatous proliferation

EPIDEMIOLOGY

2 With longer life expectancy, the incidence of vision impairment from macular diseases increased 62% from 1990 to 2010.[6] AMD is identified as the leading cause of vision impairment in the industrialized world and a top cause of blindness worldwide, in addition to diabetic retinopathy, glaucoma, cataracts, and under-correction of refraction error.[7-9] Drusen development and AMD diagnosis can occur at any age, although usually after the age of 50 years. The prevalence of AMD is 8.69% for adults 45 to 85 years of age.[10] Rates of AMD increase nonlinearly with age affecting 6% to 10% of people aged 65 years or older and more than 20% to 25% of who have reached the age of 75 years.[11,12]

Dry AMD is the most common type diagnosed in 80% to 90% of patients and 10% to 20% may progress to wet AMD.[7,11] The more severe wet AMD is associated with progressive vision loss and makes up only 10% to 20% of AMD diagnoses yet is responsible for 90% of the vision loss of AMD.[8]

In the United States, 2.8 million individuals have advanced or intermediate forms of AMD, with expectations to reach 5.44 million by 2050.[10,11] Cases of early AMD in the United States totaled 9.1 million in 2010 with expectations to increase to 17.8 million by 2050.[10]

Risk Factors

3 The two most important risk factors for AMD are older age and smoking. Additional risk factors for AMD include ethnicity and genetics, both of which are nonmodifiable. In addition to smoking, modifiable risk factors include hypertension, body-mass index (BMI), and cardiovascular disease (Table 115-1).[8]

TABLE 115-1

Risk Factors for AMD

Factor		Increased Risk	Protective
Age (years)	<55		✓
	55-75	✓	
	>75	✓	
Ethnicity	European	✓	
Race[a]	White	✓	
	Black		✓
Genetics	Y402H	✓	
	ARMS2/HtrA1	✓	
	LIPC	✓	
	rs3775291	✓	
Gender[b]	Female	✓	
Smoking	Active	✓	
	History	✓	
Diet	Omega-3 fatty acids		✓
	High fat	✓	
	Lutein		✓
	Fruit and vegetables		✓
	Nitrates		✓
Physical activity			✓
Medications	Statins		✓

[a]Take into consideration race is a socially created categorization and not determinable by genetic testing.

[b]Gender nonbinary inclusive studies have not been performed; consult www.transhealth.ucsf.edu/guidelines.[34]

The risk of development of AMD increases exponentially with age, with risk at the age of 75 years 2 to 3 times that at 65 years. A 2014 worldwide meta-

analysis found a higher prevalence of AMD in European compared to Asian, Hispanic, and African populations.[6,8] The Salisbury Eye Evaluation evaluated the prevalence of AMD of White and Black Americans and found higher prevalence of large drusen, focal hyperpigmentation, and GA in white participants, suggesting there may be a mechanism of protection against fundus abnormalities in the central zone for Black participants.[9]

Genetics

Several genetic factors are associated with increasing risk, progression, and protection from AMD.[8] The complement factor H (CFH)–related gene on chromosome 1 binds to factor C3b and is involved in regulation of the innate immune system. This regulation is defective with a homozygous Y402H polymorphism of *CFH*, causing alteration at the C3b site leading to an up-regulation of inflammation, affecting vascular endothelial growth factor (VEGF) expression, and increasing the risk of AMD by 7.4-fold.[13]

Other genetic variants associated with increased risk of AMD include the ARMS2/HtrA serine peptidase 1 (*HtrA1*) genes, hepatic lipase (*LIPC*) gene, and the rs3775291 variant in the toll-like receptor 3 (*TLR3*) gene.[8,13] Despite publications suggesting genetic testing may be helpful, genetic tests are not recommended in patient care at this time because of inconclusive data.[14,15]

Smoking

Because it is a modifiable risk factor, smoking is important for health professionals to address; it is associated with an increased risk of AMD.[8] Studies have consistently found an increased risk across different populations of early, wet, and dry AMD with current smoking and former smoking within the last 20 years.[8]

Smoking cessation is a staple in the care plan for patients at risk for and with a prior diagnosis of AMD due to the ability to slow progression. The Australian government added warnings to cigarette packs regarding the risk of blindness related to data from AMD.[16] In 2014, the United States Department of Health & Human Services published a report of the damage smoking can do to health; however, the warnings on cigarettes in the United States are opposed by the tobacco industry.[17,18]

Diet

Diets higher in saturated, transunsaturated, polyunsaturated, and monounsaturated fatty acids (FAs) are associated with higher prevalence and progression of AMD compared to diets with lower intake of fat.[8] Interestingly, FA in nuts and fish was protective. Omega-3 FA intake can decrease the risk of AMD by up to 30%.[8]

Antioxidant intake has also proven important in AMD.[19] Lutein, zeaxanthin, zinc, and vitamins C and E had varying results when evaluating supplements and dietary intake. Combining types of antioxidants, through a varied diet, tends to have better results.[20-22] A recent population-based cohort study found that patients who followed a diet consisting of 200 g of vegetables per day, fruit twice daily, and fish twice a week had a significantly reduced risk of AMD.[20] Dietary nitrate intake of 142 g/day, from vegetable and nonvegetable sources, was also found to reduce incidence of early AMD.[23]

Additional Risk Factors

AMD can loosely be linked to atherosclerosis and cardiovascular disease.[8,24] Risk factors of these disease states overlap, including hypertension, which is associated with a higher incidence of wet AMD. Obesity and inactivity are also associated with increased risk of early and late AMD.[25] 3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with a potential modest reduction in risk of early AMD and a protective effect against wet AMD; the drugs show no benefit or harm with respect to risk of dry AMD.[26] Aspirin was thought to increase the chance of developing wet AMD, but results have been conflicting and the minimal increase in the risk of wet AMD is less than the benefit in using aspirin for cardiovascular disease in older adults.[8,27]

Ultraviolet radiation exposure, especially in people with light-colored eyes, has also shown an increase in the risk of AMD.[28] Thyroid dysfunction and thyroxine use have both shown an association with increased AMD diagnosis.[29] Medications have also been associated with AMD including

nitroglycerin, beta-blockers, chloroquine derivatives, and phenothiazines.[30] Environmental safety is a prudent component to evaluate due to unsafe chemicals and the need for a focus on sustainability in healthcare.[31] Pesticide exposure was correlated to AMD diagnosis in the Agriculture Health Study reporting that exposure to insecticides and herbicides is a modifiable risk factor for AMD.[32]

ETIOLOGY

AMD is a neurodegenerative disease with ocular inflammation and autoimmunity in combination with additional causes of RPE dysfunction and atrophy including the effects of aging, external environmental factors, and genetic factors.[8] Abnormal processing of complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways contribute to the detrimental changes, but the pathogenesis of AMD is not fully understood. Oxidative stress and complement activation can increase RPE secretion of VEGF-A, which is associated with angiogenesis.

Wet AMD has CNV, which are new blood vessels created in the choroidal region of the eye. There are different types of wet AMD determined by how the CNV occurs and how it affects the RPE.[8] In type 1, formerly referred to as “occult,” CNV is categorized by lesions with leakage of blood or plasma proteins from immature choroidal blood vessels that remain below the RPE.[8] The extra volume may cause pigment epithelial detachment. Type 1 can progress to type 2. In type 2, often referred to as classic, lesions push through and are visible above the RPE. Type 3 has retinal angiomatous proliferation meaning the choroidal and retinal vessels link together. Retinal macrophages are increased and are a hallmark sign of CNV.[34]

Dry AMD has been labeled a metabolic storage disease, due to the excessive buildup of lipofuscin, a nondegradable debris that accumulates in the RPE with age or other toxic accumulations between the RPE and Bruch’s membrane.[35] The deposits on the semipermeable Bruch’s membrane interfere with efflux, increasing stress and inflammation on the RPE (Fig. 115-3). This stress, in addition to cigarette smoking and aging, increases lipofuscin that interferes with lipid metabolism. The extra volume shifts the original layers of the RPE complex resulting in GA.

Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and Huntington’s disease are other common neurodegenerative diseases of aging potentially related to AMD.

A reduction in quality of life (QOL) is common with AMD.[36] Clinical depression is reported in one-third of patients, twice the rate of peers without AMD, and this risk increases as vision deteriorates.[8,37] A significant decline in participation in valued activities such as hobbies can occur, which has been found to increase the risk of depression. Additionally, a meta-analysis reported an association of AMD, specifically late AMD, with an increased risk of all-cause and cardiovascular mortality.[38]

PATHOPHYSIOLOGY

The presence and type of drusen on the retina upon examination can predict the progression of AMD. Drusen are yellow-white deposits made up of protein and lipids that appear on a layer of the retina known as the Bruch’s membrane, a thin, semipermeable membrane that operates as a basement membrane for the retinal epithelium and mediates the metabolic exchange between the retina and the choroid (Fig. 115-3). While the exact cause of drusen is unknown, several hypotheses suggest that drusen are composed of lipids and cellular debris accumulation from the rods and cones of the retina that are not fully eliminated. While drusen are not a cause of or diagnostic of AMD, the presence of drusen on examination can increase a person’s risk of developing AMD. Patients younger than 50 years should consider hereditary factors for macular disease if signs and symptoms similar to AMD are present.[8]

Drusen can be classified as hard or soft (Fig. 115-4). Drusen that are small, round, well-defined spots located far away from one another on the retina are called “hard” drusen. Hard drusen are not a large cause for concern for vision loss or AMD as they may never progress to AMD or may be slow to progress. Most people over the age of 50 years have hard drusen present on their retina, and these are considered a natural consequence of aging. Soft drusen increase the risk for AMD (specifically wet AMD); these are larger drusen, are not well-defined with blurred edges, and are often clustered closer together on the retina. The presence of large, soft drusen is associated with vision loss and an increased risk for progression to AMD. Soft drusen can also lead to RPE detachment through the disruption of the retinal layers.

Dry AMD

Atrophic or dry AMD is a painless disease of the macula resulting in a gradual loss of vision. The most common form of AMD, dry AMD can progress slowly and is less threatening to central vision loss compared to wet AMD. Dry AMD is characterized by subretinal hard and soft drusen deposits, the thinning of the macula, RPE atrophy, and hyperpigmentation of the retina. The cause of dry AMD is unknown, but studies indicate that it may be related to inflammation, genetics, and environmental factors such as smoking and diet.[24,25]

Dry AMD is usually diagnosed in patients older than 50 years. As the eye ages, the macula begins to thin and break down. Early detection, self-care, and reduction of risk factors through better diet, smoking cessation, and vitamin supplementation can help to slow progression of the disease.

Dry AMD that progresses to the advanced stage—when there is progressive and irreversible loss of RPE, choriocapillaris, and photoreceptors leading to a loss of central vision—is called GA.[39] Severe GA can also progress to wet AMD.

Dry AMD usually affects both eyes, but in some patients, only one eye is affected. Patients with dry AMD in one eye may not have noticeable symptoms because the healthier eye will overcompensate for the eye affected by AMD. The patient's peripheral vision is not affected by dry AMD, so the vision loss may not be obvious in the early stages of the disease.

Symptoms of dry AMD are as follows[39]:

- Difficulty reading or driving (eg, increasing blurriness of written words)
- Visual distortion (eg, straight lines appearing bent)
- Blurred images (eg, difficulty recognizing faces)
- Difficulty seeing in low or dim light; bright light may be needed to see better
- Decreasing central vision
- Colors may not appear as bright as they once were

Wet AMD

CNV, or exudative AMD, is typically referred to as wet AMD and is advanced AMD.[8,40] Wet AMD is characterized by the loss of central vision caused by CNV, which is the abnormal growth of new blood vessels from the choroid into the macula and retina. These abnormal blood vessels can leak blood or fluid into the retina and can form pockets of fluid between the choroid and the RPE; these can be seen as bumps in the macula and cause a disruption in central vision. The patient will see dark spots (floaters) in their central vision because of the pockets of fluid and wavy lines instead of straight lines because their macula is no longer smooth. The presence of drusen that are large and soft and RPE hyperpigmentation increases the risk of the development of wet AMD.

VEGF plays an important role in the pathogenesis of wet AMD. VEGF is a specific and potent regulator of angiogenesis and is responsible for the abnormal growth of blood vessels. One isoform, VEGF-A, is most strongly associated with angiogenesis in ocular diseases and is therefore a target for VEGF inhibitors for the treatment of wet AMD.[8,41]

Like dry AMD, wet AMD may affect one or both eyes. Once the patient has progressed to wet AMD, vision loss may be rapid if treatment is not initiated promptly to address the leaky blood vessels. Symptoms of wet AMD are similar to dry AMD and also include the presence of dark spots in the patient's central vision; peripheral vision is not affected. Patients at high risk of wet AMD should have regular eye examinations to assess functional change.

Classification of AMD

AMD can be classified using different systems. Most practitioners use the Age-Related Eye Disease Study (AREDS) classification or the more recently developed Beckman Classification system (Table 115-2), which is based on the presence and size of drusen and pigmentary changes.[8,42]

TABLE 115-2

Classification of Age-Related Macular Degeneration

Clinical Classification	Characteristics
Normal aging changes	Small drusen ≤63 µm No pigmentary abnormalities
Early AMD	Medium-sized drusen >63 µm and ≤125 µm No pigmentary abnormalities
Intermediate AMD	Large drusen >125 µm and/or any pigmentary abnormalities
Late AMD	Neovascular AMD and/or GA
AREDS Classification	
No AMD (Category 1)	No or few small drusen
Early AMD (Category 2)	Multiple small drusen Few intermediate drusen Mild abnormalities in the retinal pigment epithelium
Intermediate AMD (Category 3)	Any of the following: ○ Numerous intermediate drusen ○ At least one large drusen ○ GA
Advanced AMD (Category 4)	One or more of the following: ○ GA of the retinal pigment epithelium involving the foveal center ○ Neovascular maculopathy that includes the following: ■ CNV ■ Serous and/or hemorrhagic detachment of the neurosensory retina or retinal pigment epithelium ■ Retinal hard exudates ■ Subretinal and subretinal pigment epithelium fibrovascular proliferation ■ Disciform scar (subretinal fibrosis)

AREDS, Age-Related Eye Disease Study; AMD, age-related macular degeneration.

Early AMD

AREDS defines early AMD based on the presence of a few small (<63 µm) to medium (63-124 µm) drusen. The patient may or may not have pigment

epithelial abnormalities in the macula. Patients diagnosed with early AMD have a low risk of progressing to advanced AMD after 5 years of stable disease.[42]

Intermediate AMD

Intermediate AMD has been defined by the AREDS as having one or more large drusen (≥125 µm in diameter) or evidence of extensive medium drusen (63-124 µm) or in one or both eyes. Patients with intermediate AMD have a much greater chance of progression to advanced AMD if left untreated. If, at baseline diagnosis, drusen are present only in one eye, there is approximately an 18% chance that the disease will progress to advanced AMD after 5 years. If medium to large drusen are present in both eyes, the risk of progression to advanced AMD increases to 26% after 5 years.[42] Upon diagnosis, patients should begin a discussion with their physician about the risks and benefits of delayed progression or stabilized visual acuity with the available treatment options.

Reticular pseudodrusen, also called subretinal drusenoid deposits, may appear in patients with intermediate AMD. These are difficult to identify upon examination, and diagnosis may require the use of fundus autofluorescence, infrared reflectance, and/or spectral domain optical coherence tomography (SD-OCT). The presence of pseudodrusen is associated with the progression of intermediate AMD.[8,43-46]

Advanced AMD

AREDS defines advanced AMD as neovascular AMD or GA present in the macula. In patients with advanced AMD, at least one eye is affected, with a complete loss of visual acuity. According to AREDS, the risk of progression of visual acuity loss in the unaffected eye is 35% to 50% at 5 years.[47] Patients with GA may have a slower loss of visual acuity compared with patients with neovascular AMD.[8]

CLINICAL PRESENTATION

AMD can present without symptoms, or patients may have complaints of central vision loss, including scotoma (a dark patch in the middle of their vision), or distorted vision. Patients are typically older than 50 years. In dry AMD, patients may complain of the need for a bright light or a magnifying glass while reading or trouble seeing while driving. Wet AMD presents as metamorphopsia, the distortion of straight lines. Acute vision loss requires urgent evaluation and care.

CLINICAL PRESENTATION: Age-Related Macular Degeneration

Signs

- Distortion when viewing the Amsler grid (Fig. 115-6)
- Dilated eye examination with a slit-lamp instrument to observe and measure
  - Dry: drusen, GA present as hypopigmentation or hyperpigmentation
  - Wet: subretinal fluid or hemorrhage, which requires other diagnostic tests

Laboratory Tests

- None

Diagnosis Tests

- Subretinal evaluation using fluorescein dye retinal angiography, optical coherence tomography, or fundus autofluorescence

TREATMENT

4 The goal of treatment is to slow progression of AMD and prevent severe visual impairment or blindness. It should be noted that while pharmacotherapeutic options do exist, there is not enough supportive evidence to advocate for one treatment option over another to prevent progression to advanced AMD. For patients with intermediate AMD, studies support the use of antioxidant vitamins and minerals to slow progression to advanced AMD. In patients with wet AMD, the use of anti-VEGF agents, photodynamic therapy (PDT), and even surgery has been studied in an attempt to slow progression to vision loss. Assessment of the patient by the physician and informed discussion with the patient evaluating the risks and benefits of treatment are necessary before treatment begins.

Smoking Cessation

5 For all patients with dry AMD, smoking cessation is crucial to include as the first-line nonpharmacotherapeutic treatment option. Smoking cessation is the primary modifiable risk factor that can slow progression of AMD.

Health professionals, particularly pharmacists, can play a vital role in providing patient counseling and assistance with choosing the appropriate over-the-counter (OTC) nicotine replacement therapy (NRT) options for patients. A Cochrane review evaluated evidence supporting the effectiveness of community pharmacists and their role in helping patients achieve smoking cessation. Well-trained, community pharmacists who provide behavioral counseling and education on choosing the appropriate NRT were able to help patients achieve smoking cessation goals. In the community setting, behavioral counseling and education for at least 1 month yielded positive smoking cessation rates.[39,48] Because most smoking cessation products in the United States are widely available OTC, community pharmacists have an opportunity to make a significant impact by helping a patient choose the appropriate NRT agent and dose while also providing the necessary counseling to support the patient (see Chapter 86, “Substance-Related Disorders: Alcohol, Nicotine, and Caffeine”).

PATIENT CARE PROCESS

Patient Care Process for Management of Age-Related Macular Degeneration

Collect

- Patient characteristics (age, sex, distance from treatment center, burden of follow-up visits, satisfaction, financial burden of treatment)
- Patient history (past medical, family history of AMD, social, smoking; date, frequency, and results of past eye examinations)
- Changes in vision (see Fig. 114-3 in the Glaucoma chapter and Fig. 115-5)
- Current medications
- Objective data (see the “Clinical Presentation” box)
- Visual field changes and losses

- Macula changes

Assess

- QOL
- Vision status (general, near, distance, peripheral)
- Mental health
- Smoking status
- Current treatment
- Functional status including driving, dependency, and role difficulties and activities of daily living (ADLs)

Plan

- Drug therapy regimen designed to prevent progression of the disease and preserve visual acuity, including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 115-4)
- Referral to an ophthalmologist as needed

Implement*

- Provide patient education regarding all elements of the treatment plan
- Provide education on diet and functional/lifestyle changes, adherence to medications, and use of the Amsler grid
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, usually 4 to 8 weeks, or as needed for specific medications

Follow-up: Monitor and Evaluate

- Monitor vision with Amsler grid (Fig. 115-6)
- Visual fields and diagnostic tests
- Adverse effects to medications
- Adherence to treatment
- Functional status
- Disease/treatment burden; financial burden

Collaborate with patient, caregivers, and other healthcare professionals.

Antioxidant Vitamins and Minerals

6 Several studies looked at the benefit of antioxidant vitamins and minerals in slowing the progression of AMD.[42] These trials are based on the hypothesis that antioxidant vitamins and minerals may prevent cellular damage in the retina caused by the formation of free radicals through light absorption. Use may benefit patients the most with medium or large drusen and/or GA in at least one eye.

Patient-specific factors must be considered before recommending available antioxidant vitamins and minerals to patients with dry AMD (Table 115-3).

AREDS evaluated the effects of high doses of vitamins E, C, and beta-carotene plus zinc (once-daily doses of vitamin E 400 IU, vitamin C 500 mg, beta carotene 15 mg, zinc 80 mg as zinc oxide, and copper 2 mg as cupric oxide) in patients with AMD with an average follow-up of 6.3 years. Compared with placebo, the supplements decreased the progression to visual acuity loss significantly in patients with intermediate and advanced disease in both the wet and dry forms of AMD. Patients with mild or borderline AMD did not demonstrate a benefit. The use of zinc alone in patients with AMD has significantly lowered the risk of progression to advanced AMD.[42]

TABLE 115-3

Selected[a] Commercially Available Vitamin Products Useful in Age-Related Macular Degeneration

Brand Names	Active Ingredients	Dosage Forms	Directions
AREDS Formulation			
Preservision AREDS	Vitamin E 400 IU, vitamin C 452 mg, beta carotene 28,640 IU, zinc 69.6 mg as zinc oxide, and copper 1.6 mg as cupric oxide	Softgel, tablet	**Softgels**: 1 softgel twice daily
			Tablets: 2 tablets twice daily
AREDS 2 Formulation			
Preservision AREDS 2	Vitamin E 400 IU, vitamin C 500 mg, zinc 80 mg as zinc oxide, and copper 2 mg as cupric oxide, lutein 10 mg, zeaxanthin 2 mg	Softgel, chewable	1 softgel twice daily
Miscellaneous formulations containing components of the AREDS and AREDS 2 ingredients			
Pro-Optic	Vitamin E 200 IU, vitamin C 500 mg, zinc 25 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2 mg	Capsule	1 capsule daily
Equate Vision Formula with Lutein, Zexanthin & Omega-3 50+	Vitamin E 30 IU, vitamin C 150 mg, zinc 9 mg, copper 1 mg, omega-3 250 mg, lutein 5 mg, zexanthin 1 mg	Tablet, softgel	1 tablet/softgel daily with food
Equate Vision Formula with Lutein	Vitamin A 1,000 IU, vitamin C 200 mg, vitamin E 60 IU, zinc 40 mg, selenium 55 mcg, copper 2 mg, lutein 2 mg	Tablet	1 tablet daily
Visivite AREDS 2 Eye Vitamin	Vitamin C 500 mg, vitamin E 400 IU, zinc 40 mg as zinc oxide, copper 1 mg as copper oxide, lutein 10 mg, zeaxanthin 2 mg	Capsule	1 capsule twice daily with meals
ActiveEyes AREDS 2	Vitamin E 266 mg, vitamin C 500 mg, zinc 80 mg as zinc oxide, copper 2 mg as copper gluconate, lutein 10 mg, zeaxanthin 2 mg (per 2 capsules)	Capsule	1 capsule twice daily
EyePromise AREDS 2	Vitamin C 500 mg, vitamin D3 2,000 IU, vitamin E 400 IU, fish oil EE 250 mg, mixed tocopherols 20 mg, alpha lipoic acid 10 mg, zeaxanthin 10 mg, lutein 10 mg	Softgel	1 softgel twice daily
Viteyes Classic AREDS	Vitamin C 500 mg, vitamin E 400 IU, zinc 25 mg as zinc oxide, copper 1.2 mg as cupric	Capsule	1 capsule

2	oxide, lutein 10 mg, zeaxanthin 2 mg		twice daily with meals
Dr. Krawitz Eye Vitamins Macular Support	Vitamin E 100IU, vitamin C 500 mg, zinc 40 mg, copper 1 mg, lutein 15 mg, zeaxanthin 3 mg, calcium 115 mg, vitamin B6 20 mg, selenium 200 mcg, bilberry 50 mg, alpha lipoic acid 20 mg, grape seed extract 20 mg, L-gluthione 10 mg	Soy free, GMO free, gluten free, sugar free vegetarian capsule	2 capsules daily
MaxiVision Ocular Formula	Vitamin C 500 mg, vitamin D3 600 IU, vitamin E 400 IU, zinc 25 mg, copper 1.6 mg, lutein 20 mg, zeaxanthin 4 mg	Capsule	2 capsules per day during a meal
Systane I-Caps AREDS	Vitamin E 400 IU, vitamin C 425 mg, beta carotene 28,640 IU, zinc 69.6 mg, copper 1.6 mg	Softgel, coated tablet	1 tablet/softgel twice daily
Systane I-Caps AREDS 2	Vitamin E 400 IU, vitamin C 500 mg, zinc 25 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2 mg	Softgel, chewable tablet	1 softgel/tablet twice daily
Ocuvite Eye Vitamin & Mineral Supplement 50+	Vitamin E 20 mg, vitamin C 150 mg, zinc 9 mg, copper 1 mg, lutein 5 mg, zeaxanthin 1 mg, omega-3 fatty acids 250 mg	Softgel	1 softgel twice daily

[a]Not an all-inclusive list.

Previous studies have shown that the use of beta-carotene is associated with an increased risk of lung cancer in smokers, thus limiting its use in this population to nonsmokers only.[49] In the AREDS 2 study, beta-carotene was replaced with lutein 10 mg and zeaxanthin 2 mg; other components of the AREDS formulation of antioxidant vitamins and minerals remained the same. The replacement combination reduced the progression of AMD and therefore would be a reasonable substitute for beta-carotene in patients with AMD who smoke.[50]

The antioxidant property of saffron and its effect on visual acuity in AMD was studied in a small number of patients older than 50 years with mild-to-moderate AMD. Study participants received saffron 20 mg/day for 3 months and were followed for 6 months. Participants who received saffron and the antioxidant vitamin cocktail studied in the AREDS study demonstrated a modest improvement in visual function compared with placebo. Continued study of saffron in a larger sample of this patient population is needed to fully support its use in improving visual acuity in AMD.[51]

Specific Treatments for Wet AMD

Decisions about specific therapies for wet AMD must take into account the risks and benefits of the various therapies and the likelihood of visual recovery. Patients with smaller, more recent drusen are more likely to benefit from therapy. Therapies discussed below—VEGF inhibitors, PDT, and surgical therapy—are specific for wet AMD.

VEGF Inhibitors and Inhibitor-Like Drugs

For most patients with wet AMD and CNV, the use of intravitreal VEGF inhibitors and other inhibitor-like drugs has improved visual acuity and decreased blindness in about 50% of treated patients.[41] VEGF is a potent endothelial cell-specific mitogen and vascular permeability factor that is produced by many cells in the body including tumor cells, macrophages, and platelets.[8] As discussed earlier, VEGF-regulated CNV is a major cause of vision loss caused by the growth of new abnormal blood vessels through the Bruch membrane into the subretinal space. VEGF inhibitors play a pivotal role in preventing neovascularization in patients with wet AMD by preventing the growth of new blood vessels into the retina. Inhibition of VEGF in AMD

can limit the progression of AMD and stabilize or reverse vision loss. Early initiation of VEGF inhibitors can have a significant effect on vision outcomes. Delay in therapy after early AMD symptoms have appeared has been associated with poor vision outcomes post-VEGF inhibitor initiation.[8]

Three recombinant humanized monoclonal antibodies—bevacizumab, ranibizumab, and brolucizumab-dbll—exert their mechanism of action as VEGF inhibitors. By acting as VEGF inhibitors in AMD, these monoclonal antibodies inhibit neovascularization within the retina by preventing the growth and leakage of new blood vessels into the retina, thus slowing the loss of vision.

Bevacizumab is a humanized monoclonal antibody approved by the US Food and Drug Administration (FDA) for ovarian, non-small-cell lung, glioblastoma, and colorectal cancers and is used off label intravitreally for wet AMD. It exerts its effect on all isoforms of VEGF. Compared with ranibizumab, bevacizumab is much less expensive.[52] Structurally, ranibizumab and bevacizumab are different but related monoclonal antibodies.

Ranibizumab is a fragmented monoclonal antibody that was genetically engineered to have an increased binding affinity for all biologically active forms of VEGF, allowing for increased VEGF inhibition. This is achieved by a modification of the amino acid sequence in ranibizumab.

Studies comparing the efficacy of bevacizumab to ranibizumab given monthly or as needed have found that both drugs improve visual acuity, with no significant differences seen in efficacy.[53,54] Both drugs also demonstrated similar safety data, with no differences seen in mortality, hospitalizations, or atherothrombotic events.

Ranibizumab has been studied for efficacy in increasing and maintaining visual acuity using a treat and extend (TREX) approach to dosing compared to the traditional monthly dosing (Table 115-4). The appeal of the ranibizumab TREX approach is the reduction of office visits and cost of the medication. Visual acuity was maintained with the TREX approach in patients with wet AMD following the initial monthly injections for 3 months, and costs associated with monthly office visits for treatment and ophthalmic examinations were decreased.[55] The TREX method in patients using ranibizumab is thus preferred over monthly injections.[54,55] Premedication prior to injection is not generally necessary with bevacizumab or ranibizumab.

TABLE 115-4

Medications Used in the Treatment of Age-Related Macular Degeneration

Medication	Brand Names	Usual Doses	Notes
Antioxidant Vitamins: described in Table 115-3			
Monoclonal Antibody VEGF Inhibitors: inhibit neovascularization within the retina by preventing the growth and leakage of new blood vessels into the retina			
Bevacizumab	Avastin	Intravitreal: 1.25 mg monthly for 3 months, then may be given monthly or as needed based on monthly ophthalmic assessment	
Ranibizumab	Lucentis	Intravitreal: 0.5 mg once a month (approximately every 28 days) TREX dosing Frequency may be reduced (eg, 4-5 injections over 9 months) after the first 3 injections or may be reduced after the first 4 injections to once every 3 months if monthly injections are not feasible	A regimen averaging 4-5 doses over 9 months is expected to maintain visual acuity and an every 3-month dosing regimen has reportedly resulted in a ~5 letter (1 line) loss of visual acuity over 9 months, as compared to monthly dosing which may result in an additional ~1-2 letter gain
Ranibizumab-nuna	Byooviz	Intravitreal: 0.5 mg once a month (approximately every 28 days) TREX dosing Frequency may be reduced (eg, 4-5 injections over 9 months) after the first 3 injections or may be reduced after the first 4 injections to once every 3 months if monthly injections are not feasible	A regimen averaging 4-5 doses over 9 months is expected to maintain visual acuity and an every 3-month dosing regimen has reportedly resulted in a ~5 letter (1 line) loss of visual acuity over 9 months, as compared to monthly dosing which may result in an additional ~1-2 letter gain
Brolucizumab-dbll	Beovu	Intravitreal: 6 mg once per month (approximately every 25-31 days) for 3 months, followed by 6 mg once every 8 to 12 weeks	
Nonmonoclonal antibody VEGF inhibitors			
Aflibercept	Eylea	Intravitreal: 2 mg once every 4 weeks for the first 12 weeks, followed by 2 mg once every 8 weeks	Some patients may require every 4-week dosing after the first 12 weeks
Pegaptanib[a]	Macugen	Intravitreal: 0.3 mg once every 6 weeks	Does not improve visual acuity in patients with new-onset wet AMD

[a]Pegaptanib is not currently available in the United States.

Brolucizumab-dbll is a humanized single-chain antibody fragment that inhibits the VEGFR-1 and VEGFR-2 receptors by binding to three major VEGF-A isoforms. It is the latest VEGF inhibitor to be approved by FDA. Two studies that established efficacy of brolucizumab-dbll compared the monoclonal

antibody to aflibercept for 48 weeks. Both of the studies found brolucizumab-dbll noninferior to the control group with regard to improvement in visual acuity. Doses studied for brolucizumab-dbll were 3 mg and 6 mg given every 12 weeks following an 8-week loading dose phase. If the patient improved or remained stable, doses were continued at 12-week intervals for a total of 48 weeks; if the disease worsened, dosing intervals were reduced to every 8 weeks. The control group was administered aflibercept 2 mg every 8 weeks for the 48-week study period.[56]

In addition to being noninferior to aflibercept, brolucizumab-dbll 6 mg doses were able to maintain the dosing interval at 12 weeks in more than 50% of the study participants throughout the 48-week study period. Additionally, a statistically significant difference was observed in the decrease in visual acuity in patients treated with brolucizumab-dbll 6 mg compared to aflibercept 2 mg after week 16 of the treatment. Overall, the studies concluded that the brolucizumab-dbll treatment is noninferior to aflibercept with improving visual acuity as measured by the mean best-corrected visual acuity change from baseline.[56]

VEGF Inhibitor Biosimilars

Ranibizumab-nuna, the first biosimilar of ranibizumab, was approved by the FDA with indications of dry AMD, macular edema, and myopic CNV. Another biosimilar currently under investigation for approval is bevacizumab-vikg (ONS-5010). The indications being studied for bevacizumab-vikg are dry AMD, DME, and branch retinal vein occlusion.[57]

The VEGF inhibitor drugs aflibercept and pegaptanib are also administered intravitreally in wet AMD. These drugs are pharmacologically classified as VEGF inhibitors and are not monoclonal antibodies such as bevacizumab or ranibizumab. Aflibercept and pegaptanib are primarily used in patients who have an insufficient response in visual acuity improvement to ranibizumab and bevacizumab.

The first VEGF inhibitor approved by the FDA for use in wet AMD was pegaptanib. Pegaptanib was approved by the FDA in 2004. Randomized controlled trials at the time of approval demonstrated efficacy with the 0.3-mg dose injected into the vitreous every 6 weeks, but pegaptanib does not improve visual acuity in patients with new-onset wet AMD compared with other VEGF inhibitors.[8] For these reasons, it is rarely used in clinical practice and has been discontinued in the United States.

Aflibercept is a pan-VEGF-A and placental growth factor blocker that exerts its action in wet AMD by competing for binding with VEGF-A.[8] It was approved by the FDA in 2011.

Aflibercept is dosed by intravitreal injections of three monthly loading doses, followed by 2 mg injected intravitreally every 4 to 8 weeks. While some patients may require every 4-week injections, there was no additional efficacy noted in the clinical trials in doses administered every 4 weeks compared with every 8 weeks. Therefore, in patients receiving aflibercept 2 mg every 8 weeks, the benefit is improvement of visual acuity without the burden and risk of monthly intravitreal injections or monitoring.

Efficacy and safety tolerability are similar between the two VEGF inhibitors, with the advantage being that aflibercept had the potential for a reduced administration schedule at every 2 months and a reduced monthly cost compared with aflibercept. Overall, it is unknown if there is a standard optimal dosing schedule for VEGF inhibitors.

Adherence with these medications is imperative to maintain the visual acuity gains achieved.[58] If therapy is not continued, the gains can be lost. Counseling patients on the importance of adherence, risks of nonadherence, and options if cost is prohibitive are needed for the continued benefit of VEGF therapy.

Agents in the Pipeline

Faracimab is a new agent in development with a combined mechanism of action.[59] In addition to being a VEGF inhibitor targeting VEGF-A, faracimab also inhibits angiopoietin isoform 2 (Ang-2), which is a growth factor in the Ang-Tie pathway, a main pathway involved in angiogenesis.[60] Inhibition of Ang-2 can improve vascular permeability. Several multicenter phase 2 trials have demonstrated the efficacy of faracimab, providing a therapeutic option that may be administered less frequently than monthly ranizumab therapy and maybe more efficacious at improving visual acuity.[61-63]

An ocular implant device designed to provide continuous delivery of ranizumab has recently been approved for use in patients with dry AMD and who has received at least 2 doses of a VEGF inhibitor intravitrealy with an improved response to therapy. Once implanted, the device will deliver a

continuous dose of ranizumab. One other advantage to this device is that it only requires refilling every 6 months in a physician's office in a manner similar to receiving a traditional intravitreal injection of ranizumab.[64]

Photodynamic Therapy for Wet AMD

PDT is initiated in patients with wet AMD who fail to demonstrate an improvement in visual acuity with the use of VEGF inhibitors alone. PDT for AMD is performed by the intravenous injection of a photosensitizing dye, verteporfin, followed by activation of the dye using a photo laser applied through the use of a specialized contact lens. A physician then shines a laser into the patient's eye, focused on a localized area. The laser activates the dye, causing the formation of a thromboembolism within the abnormal blood vessels below the macula. The thromboembolism seals off the abnormal blood vessels, preventing further leakage of the fluid into the retina that is causing difficulty in vision.

PDT may be used with or without VEGF inhibitors in patients whose visual acuity has worsened while on treatment with VEGF inhibitors alone.[8] When used at least once in combination with the VEGF inhibitors ranibizumab or bevacizumab, it can help improve and maintain visual acuity with continued VEGF inhibitor administration. Several randomized controlled trials with verteporfin and ranibizumab indicate that the combination therapy of VEGF inhibitors with PDT was more effective in improving and maintaining visual acuity and required fewer PDT treatments than with PDT alone, yet more studies are needed.[8,65]

A meta-analysis of randomized clinical trials comparing the combination therapy of bevacizumab and PDT to bevacizumab monotherapy concluded that patients treated with combination PDT + bevacizumab required significantly less injections of bevacizumab with similar effects on visual acuity improvement and ocular side effects compared to bevacizumab monotherapy.[66] Results have been conflicting with aflibercept plus PDT usage and changes in visual acuity. A randomized trial was unable to demonstrate benefit in combination over monotherapy alone due to insufficient patients meeting criteria for dual therapy.

Side effects of PDT are light sensitivity for several days following the procedure and pain in the eye. Patient counseling should include instructions on avoiding exposure to direct sunlight, wearing dark sunglasses and protective clothing when outside, and using OTC analgesics such as acetaminophen for pain. Patients may experience blurry vision that is temporary and will subside. However, worsening vision or increasing eye pain should be reported to a physician.

Surgical Therapy

Management of AMD using surgical techniques is varied and requires further investigation. Surgical therapy is usually reserved in patients with substantial macular hemorrhages that lack a response to VEGF inhibitor therapy.

The most effective surgery for these patients has been the removal of submacular hemorrhages following the administration of tissue plasminogen activator (tPa) into the retina.[67] Visual acuity improves following surgery; however, it declines over time without the continued use of a VEGF inhibitor to decrease CNV.

Thermal laser photocoagulation is a surgical procedure that involves the use of a thermal laser seal to stop the leakage of fluid from abnormal blood vessel growth under the macula. The heat from the laser seals the abnormal, leaky blood vessels, preventing further fluid leakage and subsequent loss of visual acuity. The negative aspect of this procedure is that it can also destroy surrounding healthy retinal tissue as it seals the leaky blood vessels. Because of this risk, thermal laser photocoagulation is not used to seal vessels located directly under the center of the macula. Thermal laser photocoagulation does not restore vision loss in advanced AMD and should be used as early as possible in therapy to help prevent progression of the disease. Because of these limitations, thermal laser photocoagulation is rarely used in clinical practice.

Antioxidant Vitamins, Beta Carotene, and Zinc

As discussed earlier, antioxidant vitamins and minerals may be useful in delaying progression to advanced AMD in patients with the presence of drusen. The choice of vitamin formulation should be considered based on the patient's history of smoking. Smokers with AMD should be counseled to use only the vitamin formulation that contains lutein and zeaxanthin, whereas nonsmokers can use the formulations containing either beta-carotene or lutein and zeaxanthin. Attention should be paid to amount of vitamin E the patient is consuming daily to avoid vitamin E overdose with the use of other multivitamin supplements.

Daily doses should consist of vitamin C 500 mg, vitamin E 400 IU, lutein 10 mg, zeaxanthin 2 mg, zinc oxide 80 mg, and copper (cupric oxide) 2 mg. Beta-carotene 15 mg may be used in lieu of lutein and zeaxanthin in nonsmokers.

Statin Therapy

The use of statins to prevent the onset of AMD and progression of early AMD to late AMD has been evaluated in several randomized placebo-controlled studies. Epidemiologic data suggest a link between patients with atherosclerotic disease and AMD, and the use of statins may exert a protective effect in patients with AMD.[26,68] The rationale is that drusen are composed of lipid deposits that accumulate within the retinal layers. The effects of statins on drusen are hypothesized to be through a number of different mechanisms. Through the serum lipid lowering, statins may alter the formation of lipid deposits on the Bruch's membrane.[17] Statins may also exert a protective effect against atherosclerosis and AMD by preserving the vascular supply to the outer retina.[18] There may also be an intraocular anti-inflammatory effect through the inhibition of VEGF. In AMD, elevated levels of VEGF may play a role in the development of CNV. Finally, statins may interfere with secretion of metalloproteinases, which when released play a role in the rupture of lipid plaques and neovascular development.[19]

Several studies have examined the effect of statins on preventing or reducing progression of AMD to vision loss. Studies evaluating simvastatin indicated there may be a benefit in patients with early AMD; however, sample sizes were small in one study and in the largest study, 30% of patients were lost to follow-up.[17,20] In both studies, no benefit was observed in patients with advanced AMD to support statin therapy. In a small pilot study of patients with advanced AMD, intensive therapy with atorvastatin 80 mg daily indicated a possible regression in drusen size and vision improvement, but a larger study should be conducted to confirm these effects.[21]

Overall, statin therapy is not recommended for the treatment of patients with AMD alone, as results from larger studies would be needed to support use.[8] Statins may be used in AMD patients with other indications such as a diagnoses of atherosclerosis, coronary artery disease, or hyperlipidemia.

Prevention of AMD

Antioxidant vitamins and minerals have not been proven to prevent the onset of AMD in patients with risk factors such as drusen.[69] One trial indicated that there may be some benefit in the use of B vitamins in preventing the onset of AMD. The study compared folic acid 2.5 mg/day, pyridoxine 50 mg/day, and cyanocobalamin 1 mg/day to placebo in women with an increased risk of cardiovascular disease without AMD. After 7 years of follow-up, more women in the placebo group had evidence of AMD compared to the treatment group. Additional studies with larger patient populations are needed to confirm these results. However, it is promising that the use of B vitamins may be beneficial in reducing the risk of AMD in women with cardiovascular disease.[70]

Diets rich in the omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) found in fish and plant-based omega-3 FA, such as alpha-linolenic acid (ALA), may play a role in decreasing the progression to advanced AMD in patients with intermediate AMD, as seen in several subsets of studies.[8] However, there is insufficient evidence to say that dietary modification can prevent AMD formation.[8,71]

As previously discussed, smoking cessation is imperative (Table 115-1).

EVALUATION OF THERAPEUTIC OUTCOMES

The overall goal of therapy for macular degeneration is to prevent vision loss through slowing down progression of the disease and preserving visual acuity.

9 VEGF inhibitors and antioxidant vitamins and minerals are the only pharmacologic therapies available that have been shown to improve and stabilize visual acuity in patients with intermediate to advanced AMD. It is important to counsel the patient when discussing the treatment options that they are not curative and may only serve to improve visual acuity from baseline. Current pharmacologic therapy options will require repeated long-term administration to maintain visual acuity.

No pharmacologic therapy has been shown to prevent AMD in patients with high-risk factors for development. Studies are conflicting regarding the implementation of a diet high in omega-3 fatty acids such as EPA and DHA found in fish and plant-based omega 3 fatty acid supplements, such as ALA

for prevention of AMD. More studies are needed to fully support this indication.

CONCLUSION

Age-related macular degeneration remains one of the leading causes of blindness globally. Its impact on the QOL of the aging adult can be tremendous. Early detection of this disease is the key to preserving visual acuity and allows early initiation of pharmacologic therapy to help stabilize and slow vision loss.

ABBREVIATIONS

ALA	alpha-linolenic acid
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
CFH	complement factor H
CNV	choroidal neovascularization
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FA	fatty acid
FDA	Food and Drug Administration
GA	geographic atrophy
HtrA1	ARMS2/HtrA serine peptidase 1
LIPC	hepatic lipase
NRT	nicotine replacement therapy
OTC	over the counter
PDT	photodynamic therapy
QOL	quality of life
RPE	retinal pigment epithelium
TLR3	toll-like receptor 3
TREX	treat and extend
US	United States
VEGF	vascular endothelial growth factor

REFERENCES

1. Shah N, Dakin SC, Dobinson S, Tufail A, Egan CA, Anderson RS. Visual acuity loss in patients with age-related macular degeneration measured using a novel high-pass letter chart. *Br J Ophthalmol.* 2016;100(10):1346–1352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26846435. [PubMed: 26846435]

2. Hunt LA, Nijjar B, Stead A. Chapter 14: Sensory function, function related to the skin and pain: Health conditions. In: Bonder B, Bello-Haas VD, eds. *Functional Performance in Older Adults*. Philadelphia, PA: F. A. Davis Company; 2018.

3. Mathew R, Sivaprasad S, Augsburger JJ, Corrêa ZM. Retina. In: Riordan-Eva P, Augsburger JJ, eds. *Vaughan & Asbury's General Ophthalmology*. 19th ed. New York, NY: McGraw-Hill. Available at: http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.aspx?bookid=2186&sectionid=165517649.

4. Horton J. Disorders of the eye. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill. Available at: http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.aspx?bookid=2129&sectionid=192011900.

5. Chang DF. Ophthalmologic examination. In: Riordan-Eva PAJ, ed. *Vaughan & Asbury's General Ophthalmology*. 19th ed. New York, NY: McGraw-Hill. Available at: http://accessmedicine.mhmedical.com.proxy.library.vcu.edu/content.aspx?bookid=2186&sectionid=165516032.

6. 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):106. Accessed December 30, 2021. doi: 10.1016/S2214-109X(13)70145-1.

7. Chou R, Dana T, Bougatsos C, Grusing S, Blazina I. Screening for impaired visual acuity in older adults: Updated evidence report and systematic review for the US preventive services task force. *JAMA.* 2016;315(9):915–933. Accessed December 30, 2021. doi: 10.1001/jama.2016.0783.

8. American Academy of Ophthalmology Retina/Vitreous Panel. *Age-Related Macular Degeneration Preferred Practice Pattern®*. San Francisco, CA: American Academy of Ophthalmology; 2019. Updated November 2021. Available at: https://www.aao.org/Assets/ca4e92da-1e00-470b-aa28-56ed2bac2efb/637714766764570000/age-related-macular-degeneration-ppp-2021-update-pdf.

9. Bressler SB, Muñoz B, Solomon SD, West SK. Racial differences in the prevalence of age-related macular degeneration: The salisbury eye evaluation (SEE) project. *Arch Ophthalmol.* 2008;126(2):241–245. Accessed December 30, 2021. doi: 10.1001/archophthalmol.2007.53.

10. Jonas JB, Bourne RRA, White RA, et al. Visual impairment and blindness due to macular diseases globally: A systematic review and meta-analysis. *Am J Ophthalmol.* 2014;158(4):808–815. Accessed December 30, 2021. doi: 10.1016/j.ajo.2014.06.012.

11. Al-Zamil WM, Yassin SA. Recent developments in age-related macular degeneration: A review. *Clin Interv Aging*. 2017;12:1313. Accessed December 30, 2021. doi: 10.2147/CIA.S143508.

12. Kahn HA, Leibowitz HM, Ganley JP, et al. The framingham eye study. I. Outline and major prevalence findings. *Am J Epidemiol.* 1977;106(1):17–32. Accessed December 30, 2021. [PubMed: 879158]

13. Kumaramanickavel G. Age-related macular degeneration: Genetics and biology. *Asia Pac J Ophthalmol (Phila).* 2016;5(4):229–235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27488064. [PubMed: 27488064]

14. Chew EY, Klein ML, Clemons TE, Agrón E, Abecasis GR. Genetic testing in persons with age-related macular degeneration and the use of the AREDS supplements: To test or not to test? *Ophthalmology*. 2015;122(1):212–215. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642014010124. [PubMed: 25456150]

15. Wittes J, Musch DC. Should we test for genotype in deciding on age-related eye disease study supplementation? *Ophthalmology*. 2015;122(1):3–5. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642014010392. [PubMed: 25542537]

16. Adams A, Gelles EB. *Letters*. New York, NY: Library of America; 2016;275:1386–1387. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1772857/.

17. US Department of Health & Human Services. The health consequences of Smoking—50 years of progress: A report of the surgeon general, 2014 SurgeonGeneral.gov. Available at: https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html. Updated 2014. Accessed

December 30, 2021.

18. Products CfT. Labeling—cigarette graphic health warnings. Web site. Available at: https://www.fda.gov/tobaccoproducts/labeling/labeling/ucm257774.htm. Accessed December 30, 2021.

19. Ranard KM, Jeon S, Mohn ES, Griffiths JC, Johnson EJ, Erdman JW. Dietary guidance for lutein: Consideration for intake recommendations is scientifically supported. *Eur J Nutr.* 2017;56(suppl 3):37–42. Accessed December 30, 2021. doi: 10.1007/s00394-017-1580-2.

20. de Koning-Backus APM, Buitendijk GHS, Kiefte-de Jong JC, et al. Intake of vegetables, fruit, and fish is beneficial for age-related macular degeneration. *Am J Ophthalmol.* 2018. Accessed December 30, 2021. doi: 10.1016/j.ajo.2018.09.036.

21. Chew EY, Clemons TE, Sangiovanni JP. 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): Available at: http://parlinfo.aph.gov.au/parlInfo/search/display/display.w3p;query=library/jrnart/2465549.

22. Zampatti S, Ricci F, Cusumano A, Marsella LT, Novelli G, Giardina E. Review of nutrient actions on age-related macular degeneration. *Nutr Res.* 2014;34(2):95–105. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0271531713002674. [PubMed: 24461310]

23. Gopinath B, Liew G, Kifley A, et al. Association of dietary nitrate intake with the 15-year incidence of age-related macular degeneration. *J Acad Nutr Diet.* 2018. Available at: https://jandonline.org/article/S2212-2672(18)30276-4/fulltext.

24. Wu J, Uchino M, Sastry SM, Schaumberg DA. Age-related macular degeneration and the incidence of cardiovascular disease: A systematic review and meta-analysis. *PLoS ONE.* 2014;9(3):e89600. Available at: https://www.openaire.eu/search/publication?articleId=dedup_wf_001::591efe6bcfc631a2f27e50df59cf19dc. [PubMed: 24681973]

25. McGuinness MB, Le J, Mitchell P, et al. Physical activity and age-related macular degeneration: A systematic literature review and meta-analysis. *Am J Ophthalmol.* 2017;180:29–38. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0002939417302180. [PubMed: 28549846]

26. Ma L, Wang Y, Du J, Wang M, Zhang R, Fu Y. The association between statin use and risk of age-related macular degeneration. *Sci Rep.* 2015;5:18280. Accessed December 30, 2021. doi: 10.1038/srep18280.

27. Ye J, Xu YF, He JJ, Lou LX. Association between aspirin use and age-related macular degeneration: A meta-analysis. *Invest Ophthalmol Vis Sci.* 2014;55(4):2687–2696. doi: 10.1167/iovs.13-13206.

28. Klein BEK, Howard KP, Iyengar SK, et al. Sunlight exposure, pigmentation, and incident age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2014;55(9):5855–5861. Accessed December 30, 2021. [PubMed: 25125603]

29. Gopinath B, Liew G, Kifley A, Mitchell P. Thyroid dysfunction and ten-year incidence of age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2016;57(13):5273–5277. Accessed December 30, 2021. doi: 10.1167/iovs.16-19735.

30. Klein R, Myers CE, Klein BE. Vasodilators, blood pressure-lowering medications, and age-related macular degeneration: The Beaver Dam Eye Study [published correction appears in *Ophthalmology*. 2016 Apr;123(4):923]. *Ophthalmology*. 2014;121(8):1604–1611. doi: 10.1016/j.ophtha.2014.03.005.

31. Modenese A, Gobba F. Macular degeneration and occupational risk factors: A systematic review. *Int Arch Occup Environ Health*. 2019;92(1):1–11. doi: 10.1007/s00420-018-1355-y.

32. Montgomery MP, Postel E, Umbach DM, et al. Pesticide use and age-related macular degeneration in the agricultural health study. *Environ Health Perspect*. 2017;125(7):077013. Accessed December 30, 2021. doi: 10.1289/EHP793.

33. Center of Excellence for Transgender Health, Department of Family and Community Medicine, University of California San Francisco, ed. *Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people*. 2nd ed.; 2016. Deutsch M.B., ed. Available at:

www.transhealth.ucsf.edu/guidelines.

34. Jager MJ. Macrophages and macular degeneration. *J Ophthalmic Vis Res.* 2014;9(1):1–2. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074466/. [PubMed: 24982724]

35. Zając-Pytrus HM, Pilecka A, Turno-Kręcicka A, Adamiec-Mroczek J, Misiuk-Hojło M. The dry form of age-related macular degeneration (AMD): The current concepts of pathogenesis and prospects for treatment. *Adv Clin Exp Med.* 2015;24(6):1099–1104. doi: 10.17219/acem/27093.

36. Chatziralli I, Mitropoulos P, Parikakis E, Niakas D, Labiris G. Risk factors for poor quality of life among patients with age-related macular degeneration. *Semin Ophthalmol.* 2017;32(6):772–780. Available at: https://doi-org.proxy.library.vcu.edu/10.1080/08820538.2016.1181192. [PubMed: 27648680]

37. Dillon L, Gandhi S, Tang D, et al. Perspectives of people with late age-related macular degeneration on mental health and mental wellbeing programmes: A qualitative study. *Ophthalmic Physiol Opt.* 2021;41(2):255–265. doi: 10.1111/opo.12779.

38. Xin X, Sun Y, Li S, Xu H, Zhang D. Age-related macular degeneration and the risk of all-cause and cardiovascular mortality: A meta-analysis of cohort studies. *Retina*. 2018;38(3):497–507. doi: 10.1097/IAE.0000000000001741.

39. Sadda SR, Chakravarthy U, Birch DG, Staurenghi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina (Philadelphia, Pa.).* 2016;36(10):1806–1822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27652913. [PubMed: 27652913]

40. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group [published correction appears in Ophthalmology. 2020 Oct;127(10):1434-1435]. *Ophthalmology*. 2020;127(5):616–636. doi: 10.1016/j.ophtha.2019.11.004.

41. Sloan FA, Hanrahan BW. The effects of technological advances on outcomes for elderly persons with exudative age-related macular degeneration. *JAMA Ophthalmology*. 2014;132(4):456–463. http://dx.doi.org/10.1001/jamaophthalmol.2013.7647. doi: 10.1001/jamaophthalmol.2013.7647.

42. 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. Accessed December 30, 2021. [PubMed: 11594942]

43. Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF. Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: Morphology, prevalence, topography, and biogenesis model. *Retina (Philadelphia, Pa.).* 2013;33(2):265–276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23266879. [PubMed: 23266879]

44. Sarks J, Arnold J, Ho I, Sarks S, Killingsworth M. Evolution of reticular pseudodrusen. *Br J Ophthalmol.* 2011;95(7):979–985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21109695. [PubMed: 21109695]

45. Zweifel SA, Imamura Y, Spaide TC, Fujiwara T, Spaide RF. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology*. 2010;117(9):1775–1781. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0161642010000552. [PubMed: 20472293]

46. Ueda-Arakawa N, Ooto S, Tsujikawa A, Yamashiro K, Oishi A, Yoshimura N. Sensitivity and specificity of detecting reticular pseudodrusen in multimodal imaging in Japanese patients. *Retina (Philadelphia, Pa.).* 2013;33(3):490–497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23403515. [PubMed: 23403515]

47. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS report no. 18. *Arch Ophthalmol*. 2005;123(11):1570–1574. Available at: http://dx.doi.org/10.1001/archopht.123.11.1570. [PubMed: 16286620]

48. Sinclair HK, Bond CM, Stead LF. Community pharmacy personnel interventions for smoking cessation. *Cochrane Database Syst Rev.* 2004;1:CD003698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14974031.

49. Druesne-Pecollo N, Latino-Martel P, Norat T, et al. Beta-carotene supplementation and cancer risk: A systematic review and meta-analysis of randomized controlled trials. *Int J Cancer.* 2010;127(1):172–184. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.25008.

50. Chew EY, Clemons T, et al. AREDS2 Research Group. The age-related eye disease study 2 (AREDS2): Study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282–2289. [PubMed: 22840421]

51. Broadhead GK, Grigg JR, McCluskey P, Hong T, Schlub TE, Chang AA. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: A randomised clinical trial. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. 2018;1–10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30343354.

52. Brown GC, Brown MM, Rapuano S, Boyer D. Cost-utility analysis of VEGF inhibitors for treating neovascular age-related macular degeneration. *Am J Ophthalmol.* 2020;218:225–241. doi: 10.1016/j.ajo.2020.05.029.

53. 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. Available at: doi: 10.1016/j.ophtha.2014.07.041. https://www.clinicalkey.es/playcontent/1-s2.0-S016164201400685X.

54. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122(12):2514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26391465. [PubMed: 26391465]

55. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(1):57–65. Available at: https://www.sciencedirect.com/science/article/pii/S0161642017310254. [PubMed: 28893454]

56. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. *Ophthalmology*. 2020;127(1):72–84. doi: 10.1016/j.ophtha.2019.04.017.

57. Outlook Therapeutics. ONS-5010/LYTENAVATM OVERVIEW. https://outlooktherapeutics.com/lytenava-overview/. Published 2019. Accessed December 7, 2021.

58. Ehlken C, Helms M, Böhringer D, Agostini HT, Stahl A. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. *Clin Ophthalmol.* 2018;12:13–20. [PubMed: 29339917]

59. Nicolò M, Ferro Desideri L, Vagge A, Traverso CE. Faricimab: An investigational agent targeting the Tie-2/angiopoietin pathway and VEGF-A for the treatment of retinal diseases. *Expert Opin Investig Drugs*. 2021;30(3):193–200. doi: 10.1080/13543784.2021.1879791.

60. Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of angiopoietin-2 in vascular physiology and pathophysiology. *Cells*. 2019;8(5):471. https://doi.org/10.3390/cells8050471. [PubMed: 31108880]

61. Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens of faricimab vs ranibizumab in neovascular age-related macular degeneration: The AVENUE Phase 2 randomized clinical trial. *JAMA Ophthalmol.* 2020;138(9):955–963. doi: 10.1001/jamaophthalmol.2020.2685.

62. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of Every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: The STAIRWAY Phase 2 randomized clinical trial. *JAMA Ophthalmol.* 2020;138(9):964–972. doi: 10.1001/jamaophthalmol.2020.2699.

63. Sahni J, Patel SS, Dugel PU, Khanani AM, Jhaveri CD, Wykoff CC, Hershberger VS, Pauly-Evers M, Sadikhov S, Szczesny P, Schwab D, Nogoceke E, Osborne A, Weikert R, Fauser S. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*. 2019;126(8):1155–1170. doi: 10.1016/j.ophtha.2019.03.023. Epub 2019 Mar 21. PMID: 30905643.

64. SUSVIMO [package insert]. South San Francisco, CA: Genentech, Inc: 2021. Accessed December 30, 2021. Available at: https://www.susvimo-hcp.com/.

65. Su Y, Wu J, Gu Y. Photodynamic therapy in combination with ranibizumab versus ranibizumab monotherapy for wet age-related macular degeneration: A systematic review and meta-analysis. *Photodiagnosis Photodyn Ther.* 2018;22:263–273. doi: 10.1016/j.pdpdt.2018.05.002.

66. Wei Q, Liu J, Liu Q, et al. Combination of bevacizumab and photodynamic therapy vs. bevacizumab monotherapy for the treatment of wet age-related macular degeneration: A meta-analysis of randomized controlled trials. *Exp Ther Med.* 2018;16(2):1187–1194. doi: 10.3892/etm.2018.6305.

67. Chang W, Garg SJ, Maturi R, et al. Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic displacement for age-related macular degeneration. *Am J Ophthalmol.* 2014;157(6):1250–1257. Available at: https://www.clinicalkey.es/playcontent/1-s2.0-S0002939414000701. [PubMed: 24531021]

68. Vavvas DG, Daniels AB, Kapsala ZG, et al. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. *EBioMedicine*. 2016;5:198–203. Available at: https://www.sciencedirect.com/science/article/pii/S2352396416300299. [PubMed: 27077128]

69. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev.* 2017;7:CD000253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28756617. [PubMed: 28756617]

70. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, vitamin B6, and vitamin B12 in combination and age-related macular degeneration in a randomized trial of women. *Arch Intern Med.* 2009;169(4):335–341. [PubMed: 19237716]

71. Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration. *The Cochrane Database of Syst Rev.* 2015;(4):CD010015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25856365.

SELF-ASSESSMENT QUESTIONS

1. Which of the following describe the pathophysiology of dry AMD?
   A. Detachment of the RPE cells
   B. Choroidal neovascularization below the RPE
   C. Lipid deposits on Bruch's membrane
   D. Retinal angiomatous proliferation
2. At what age is AMD the most prevalent?
   A. >50
   B. <50
   C. >65
   D. >75

3. What is a common presenting sign of wet AMD?

   A. Metamorphopsia

   B. Difficulty reading

   C. Trouble driving

   D. Decreased peripheral vision

4. The presence of which sign of AMD indicates dry AMD?

   A. Choroidal neovascularization

   B. Increased VEGF-A

   C. Drusen

   D. RPE detachment

5. For patients at risk and diagnosed with AMD, what lifestyle modification can prevent the progression?

   A. Exercise

   B. Vegetarian lifestyle

   C. Multivitamin use

   D. Smoking cessation

6. Which type of drusen are concerning for the progression of AMD?

   A. Hard

   B. Soft

   C. Small

   D. Medium

7. What pathophysiologic change is a target for medication treatment for AMD?

   A. Angiogenesis

   B. Drusen formation

   C. Inflammation

   D. Thinning macula

8. The therapeutic goals in the treatment of macular degeneration are centered toward:

   A. Reversing the presence of hard, yellow drusen on the surface of the macula

   B. Encouraging choroidal neovascularization to maintain visual acuity

   C. Maintaining visual acuity through preservation of central vision

D. Slowing the progression of the disease through the conversion of soft drusen to hard drusen

9. When considering treatment options for a patient with age-related macular degeneration (AMD), which factors about the patient are important to assess?

   A. Type of AMD, smoking status, gender

   B. Type of AMD, age, gender

   C. Type of AMD, smoking status, presence of renal disease

   D. Type of AMD, smoking status, presence of central vision

10. Identify the initial therapeutic options for age-related macular degeneration. MS is a 60-year-old male who was recently diagnosed with intermediate dry age-related macular degeneration (AMD) in both eyes. MS has a history of hyperlipidemia, hypertension, and type 2 diabetes. He is a current smoker at ½ ppd. Medications are atorvastatin 20 mg po daily, lisinopril 20 mg po daily, metformin 1,000 mg po BID, and sitagliptin 100 mg po daily. What should the physician prescribe MS as initial therapy for his dry AMD?

   A. Discontinue the atorvastatin, start an AREDS multivitamin daily, and counsel him on smoking cessation to slow down progression of AMD.

   B. Start an AREDS multivitamin daily, counsel him on smoking cessation, and begin treatment with bevacizumab intravitreally to slow down progression of AMD.

   C. Start an AREDS 2 multivitamin daily, counsel him on smoking cessation, and continue atorvastatin to slow down progression of AMD.

   D. Start an AREDS 2 multivitamin daily, counsel him on smoking cessation, and recommend photodynamic therapy to slow down progression of AMD.

11. A patient comes into the pharmacy and asks which vitamin they should take to prevent the diagnosis of AMD. What information do you share with the patient regarding prevention of AMD?

   A. Vitamins play no role in prevention of AMD and should not be used.

   B. Only the Preservision AREDS 2 can be used for prevention.

   C. Specific antioxidants show some role for certain patients.

   D. Any multivitamin that contains beta carotene can be used.

12. What expectations can a patient started on bevacizumab therapy have related to progression of AMD?

   A. Improved visual acuity

   B. Cure

   C. No longer need reading glasses

   D. Restoration of vision to prediagnosis

13. A patient is started on a multivitamin with antioxidants and ranibizumab TREX dosing. This patient is also enrolled in a smoking cessation program and currently using nicotine patches. What monitoring should occur?

   A. Amsler grid

   B. Liver function tests

   C. Serum creatinine

D. Cholesterol

14. You are counseling a patient with wet AMD after a PDT session. This patient receives combination therapy of PDT with bevacizumab. She is 65 years old, has Type 2 diabetes and hypertension. She is obese and is a social smoker and drinker. What counseling can you provide to her?

    A. Expect improved visual acuity with combination therapy

    B. Weight loss will allow a greater visual acuity improvement

    C. Smoking cessation is the best step she can take

    D. Thermal laser photocoagulation is the next step

15. A patient explains that his insurance coverage has lapsed and he is unable to afford his medications. What options does he have to prevent progression of his disease?

    A. Consider TREX

    B. Take a break from therapy until coverage is found

    C. Reach out to manufacturers for patient assistant programs

    D. Use a multivitamin

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Debris accumulates on Bruch's membrane in dry AMD. See the "Pathophysiology" section of this chapter for more information.

2. **D.** The incidence of AMD increases nonlinearly with age with the highest percentage in patients >75 years of age. See the "Epidemiology" section of of this chapter for more information.

3. **A.** Line distortion is a common finding with wet AMD. See the "Clinical Presentation" box for more information.

4. **C.** Dry AMD is characterized by drusen development. See the "Pathophysiology" section of this chapter for more information.

5. **D.** Smoking cessation has shown an increased risk of 32% of diagnosis of AMD and is associated with the progression and diagnosis of all types of AMD. For more information, see the "Risk Factors" section of this chapter.

6. **B.** Hard drusen are considered a normal part of aging. Large and soft drusen are markers for progression of AMD. See the "Pathophysiology" section of this chapter for more information.

7. **A.** Angiogenesis is responsible for the abnormal growth of blood vessels and is targeted by VEGF inhibitor therapy. See the "Treatment" section of this chapter for more information.

8. **C.** The main goal of therapy for age-related macular degeneration is the prevention of central vision loss by slowing down the progression of the disease and preserving visual acuity. See the "Treatment" section of this chapter for more information.

9. **D.** The type of AMD, whether the patient is a smoker, and the degree of central vision loss will guide the provider in choosing the type of long-term therapy for the patient to preserve visual acuity. See the "Treatment" section of this chapter for more information.

10. **C.** The most important therapeutic recommendation for this dry AMD patient is smoking cessation. The patient should be counseled about the importance of smoking cessation to prevent dry AMD progression and preserve vision. The AREDS 2 multivitamin and antioxidant formula contains lutein and zeaxanthin, which replaced beta carotene that has been found in other studies to be associated with an increased risk of lung cancer in smokers. The statin does not have any proven benefit in decreasing the formulation of drusen in a patient with macular degeneration; however, it is beneficial to this patient due to his current medical history of hyperlipidemia. See the "Treatment" section of this chapter for more information.

11. **C.** Vitamins have shown benefit for patients with intermediate- or large-sized drusen and GA in at least one eye. For more information, see the "Antioxidant Vitamins and Minerals" section of this chapter.

12. **A.** VEGF inhibitors have only shown preservation of improved and stabilized visual acuity in AMD. There is no cure for AMD. For more information see the "Evaluation of Therapeutic Outcomes" section of this chapter.

13. **A.** Ranibizumab is an intravitreal injection with expected outcomes of improved and maintained visual acuity measured by an Amsler grid. For more information, see the "Patient Care Process" and "Treatment" sections of this chapter.

14. **C.** Regardless of therapy chosen, smoking cessation is the best way to prevent progression and allow improvement in visual acuity. For more information see the "Treatment" section of this chapter.

15. **C.** Adherence is imperative for the treatment of AMD. Maintaining any visual acuity improvement requires adherence. See the "Treatment" section of this chapter for more information.