Age-Related Macular Degeneration

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Age-related macular degeneration is the leading cause of irreversible blindness in people 50 years of age or older in the developed world.\textsuperscript{1,2} More than 8 million Americans have age-related macular degeneration, and the overall prevalence of advanced age-related macular degeneration is projected to increase by more than 50\% by the year 2020.\textsuperscript{3} Recent advances in clinical research have led not only to a better understanding of the genetics and pathophysiology of age-related macular degeneration but also to new therapies designed to prevent and help treat it. This article reviews the clinical and histopathological features of age-related macular degeneration, as well as its genetics and epidemiology, and discusses current management options and research advances.

Normal Retinal Architecture

The macula is the central, posterior portion of the retina (Fig. 1A). It contains the densest concentration of photoreceptors within the retina and is responsible for central high-resolution visual acuity, allowing a person to see fine detail, read, and recognize faces. Posterior to the photoreceptors lies the retinal pigment epithelium. It is part of the blood–ocular barrier and has several functions, including photoreceptor phagocytosis, nutrient transport, and cytokine secretion. Posterior to the retinal pigment epithelium lies Bruch’s membrane, a semipermeable exchange barrier that separates the retinal pigment epithelium from the choroid, which supplies blood to the outer layers of the retina (Fig. 1B).\textsuperscript{4}

Changes with Age

With age, one change that occurs within the eye is the focal deposition of acellular, polymorphous debris between the retinal pigment epithelium and Bruch’s membrane. These focal deposits, called drusen, are observed during funduscopic examination as pale, yellowish lesions and may be found in both the macula and peripheral retina (Fig. 2A). Drusen are categorized as small (<63 μm in diameter), medium (63 to 124 μm), or large (>124 μm) on the basis of studies that classified the grade of age-related macular degeneration.\textsuperscript{5,6} On ophthalmoscopic examination, the diameter of large drusen is roughly equivalent to the caliber of a retinal vein coursing toward the optic disk. Drusen are also categorized as hard or soft on the basis of the appearance of their margins. Hard drusen have discrete margins; conversely, soft drusen generally have indistinct edges, are usually large, and can be confluent.\textsuperscript{5}

Pathophysiology of Age-Related Macular Degeneration

The clinical hallmark and usually the first clinical finding of age-related macular degeneration is the presence of drusen. In most cases of age-related macular degener-
peration, drusen are present bilaterally. However, an eye with only a few small, hard drusen is not considered to have age-related macular degeneration, since drusen are ubiquitous in people over 50 years of age and are considered a part of normal aging.

Excess drusen, however, can lead to damage to the retinal pigment epithelium. As recently reviewed by de Jong, damage to the retinal pigment epithelium and a chronic aberrant inflammatory response can lead to large areas of retinal atrophy (called geographic atrophy), the expression of angiogenic cytokines such as vascular endothelial growth factor (VEGF), or both. Abnormalities in collagen or elastin in Bruch’s membrane, the outer retina, or the choroid may also predispose some people to this process. Consequently, choroidal neovascularization develops and is accompanied by increased vascular permeability and fragility. Choroidal neovascularization may extend anteriorly through breaks in Bruch’s membrane and lead to subretinal hemorrhage, fluid exudation, lipid deposition, detachment of the retinal pigment epithelium from the choroid, fibrotic scars, or a combination of these findings.

Although multiple classification systems for age-related macular degeneration exist, the classification proposed by the Age-Related Eye Disease Study, a trial sponsored by the National Institutes of Health (NIH), is now increasingly used (Fig. 2). Early age-related macular degeneration (Fig. 2A) is characterized by the presence of a few (<20) medium-size drusen or retinal pigmentary abnormalities. Intermediate age-related macular degeneration (Fig. 2B) is characterized by at least one large druse, numerous medium-size drusen, or geographic atrophy that does not extend to the center of the macula. Advanced or late age-related macular degeneration can be either non-neovascular (dry, atrophic, or nonexudative) or neovascular (wet or exudative). Advanced nonneovascular age-related macular degeneration (Fig. 2C) is characterized by drusen and geographic atrophy extending to the center of the macula. Advanced neovascular age-related macular degeneration (Fig. 2D and 3A) is characterized by choroidal neovascularization and its sequelae.

Specific ophthalmic imaging techniques such as intravenous fluorescein angiography or indocyanine green angiography can augment clinical examination by identifying and characterizing choroidal neovascular lesions (Fig. 3B and 3C). Optical coherence tomography is noninvasive and can help elucidate retinal abnormalities by creat-
ing a cross-sectional image of the retina with the use of reflecting light rays (Fig. 1C and 3D).4

In early age-related macular degeneration, visual loss is generally mild and often asymptomatic. However, some symptoms may occur, including blurred vision, visual scotomas, decreased contrast sensitivity, abnormal dark adaptation (difficulty adjusting from bright to dim lighting), and the need for brighter light or additional magnification to read small print. Gradual, insidious visual loss with central or pericentral visual scotomas typically develops in patients who have advanced non-neovascular age-related macular degeneration, usually over the course of months to years.39 Conversely, patients with neovascular age-related macular degeneration can have sudden, profound visual loss within days to weeks as a result of subretinal hemorrhage or fluid accumulation secondary to choroidal neovascularization.4,20 Although neovascular age-related macular degeneration represents only 10 to 15% of the overall prevalence of age-related macular degeneration, it is responsible for more than 80% of cases of severe visual loss or legal blind-

<table>
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<tr>
<th>A</th>
<th>Early AMD</th>
<th>B</th>
<th>Intermediate AMD</th>
<th>C</th>
<th>Advanced Non-neovascular AMD</th>
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<th>Advanced Neovascular AMD</th>
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<tr>
<td><strong>Fundus</strong></td>
<td><img src="image1" alt="Early AMD Fundus" /></td>
<td><img src="image2" alt="Intermediate AMD Fundus" /></td>
<td><img src="image3" alt="Advanced Non-neovascular AMD Fundus" /></td>
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<td><strong>Histopathological Features</strong></td>
<td><img src="image5" alt="Early AMD Histopathological Features" /></td>
<td><img src="image6" alt="Intermediate AMD Histopathological Features" /></td>
<td><img src="image7" alt="Advanced Non-neovascular AMD Histopathological Features" /></td>
<td><img src="image8" alt="Advanced Neovascular AMD Histopathological Features" /></td>
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<td><strong>Clinical Features</strong></td>
<td>Presence of a few medium-size drusen</td>
<td>Presence of at least one large druse</td>
<td>Drusen and geographic atrophy extending to the center of the macula</td>
<td>Choroidal neovascularization and any of its potential sequelae, including subretinal fluid, lipid deposition, hemorrhage, retinal pigment epithelium detachment and a fibrotic scar</td>
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<td><strong>Current Management</strong></td>
<td>Lifestyle and dietary modifications (e.g., cessation of tobacco use, increased dietary intake of antioxidants, control of blood pressure and body-mass index)</td>
<td>Supplementation according to the Age-Related Eye Disease Study, if the other eye has early or intermediate AMD</td>
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Figure 2. Classification of Age-Related Macular Degeneration (AMD).

Column A shows medium-size drusen (arrows) in early AMD, and Column B shows a large druse (arrows) in intermediate AMD. In Column C, a photograph of the fundus shows geographic atrophy (white arrow), and a histopathological photograph shows geographic atrophy with loss of Bruch’s membrane (black arrow). In Column D, the photograph of the fundus with neovascular age-related macular degeneration shows subretinal hemorrhage (blue arrow) and choroidal neovascularization (white arrow), and the histopathological photograph shows choroidal neovascularization (black arrow). (Images courtesy of Mort Smith, M.D., and Deepak Edward, M.D.)
ness (i.e., visual acuity of 20/200 or worse) resulting from age-related macular degeneration.

Since symptoms of age-related macular degeneration often vary, each eye should be examined carefully (with the other eye covered) by measuring visual acuity and by checking for subtle distortions on an Amsler grid, a square arrangement of vertical and horizontal lines that helps to assess a person's central visual field (Fig. 4). Scotomas and visual distortions may be manifested as perceived breaks, waviness, or missing portions of the lines of the grid. Many patients are unaware of these subtle changes in vision, so periodic examinations by vitreoretinal specialists are of paramount importance to help detect neovascular age-related macular degeneration, since early identification and treatment can lead to better visual outcomes. Although most people with advanced age-related macular degeneration do not become completely blind, visual loss often markedly reduces the quality of life and is associated with disability and clinical depression in up to one third of patients, even if only one eye is affected. Patients with age-related macular degeneration should be monitored for these issues throughout their care. Once advanced age-related macular degeneration develops in one eye, there is a substantial chance (43%, according to one report) of its development in the other eye within 5 years. The risk of legal blindness in both eyes for a person with unilateral visual loss from neovascular age-related macular degeneration may be approximately 12% over a period of 5 years.

**RISK FACTORS**

Several clear risk factors for the development and progression of age-related macular degeneration have been established, including advanced age, white race, heredity, and a history of smoking (Table 1). Advancing age is associated with sharp rises in the incidence, prevalence, and progres-
Age-related macular degeneration is more common in whites than in blacks. Hispanic and Chinese persons seem to have a lower prevalence of age-related macular degeneration than whites but a higher prevalence than blacks.

Over a 5-year period, incident age-related macular degeneration occurs in an estimated 1% of American adults who are 43 to 86 years of age. Epidemiologic studies of Australian, European, and Japanese subjects have shown similar incidence and prevalence rates.

Although twin studies and familial aggregation analyses have provided clear evidence of its heritability, genetic studies of age-related macular degeneration have been historically challenging. Age-related macular degeneration is manifested relatively late in life and is characterized by multiple heterogeneous phenotypes. This can limit clinical research to the study of a single generation, since often the parents of patients are deceased, and the children of patients are generally too young to have manifestations of the disease.

In 2005, using DNA-sequence data from the Human Genome Project, three independent groups reported that a polymorphism (Tyr402His) in the complement factor H (CFH) gene, located on chromosome 1 (1q31), substantially increases the risk of age-related macular degeneration in whites. These studies suggest that one copy of the Tyr402His polymorphism increases the risk of age-related macular degeneration by a factor of 2.1 to 4.6 and that two copies increase the risk by a factor of 3.3 to 7.4 in whites. CFH, a major inhibitor of the complement system, is synthesized within the macula and is present within drusen.

Other polymorphisms in CFH besides Tyr402His appear to increase the risk of age-related macular degeneration in Asians. In addition, certain polymorphisms in the complement factor B (CFB) and C2 genes have also been associated with an increased risk of the development of age-related macular degeneration. Taken together, the data suggest that polymorphisms in CFH, CFB, and C2 genes may account for nearly 75% of cases of age-related macular degeneration. These studies clearly demonstrate that the

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Table 1. Risk Factors for Age-Related Macular Degeneration.

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Among people 75 years or older. Similarly, the prevalence of advanced age-related macular degeneration increased from 0.1% among people 43 to 54 years old to 7.1% among people 75 years or older. Age-related macular degeneration is more common in whites than in blacks. Hispanic and Chinese persons seem to have a lower prevalence of age-related macular degeneration than whites but a higher prevalence than blacks.

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complement system is a major factor in the development of age-related macular degeneration.

The Ala69Ser polymorphism of another gene, the age-related maculopathy susceptibility 2 gene (ARMS2, also known as LOC387715), located on chromosome 10 (10q26), has also been strongly implicated in the development of age-related macular degeneration, independently of CFH. ARMS2 codes for a protein (whose function remains unknown) that has been localized to mitochondria and is expressed in the retina. Persons homozygous for risk alleles in both CFH (Tyr402His) and ARMS2 (Ala69Ser) appear to be at dramatically increased risk for age-related macular degeneration (odds ratio, 57.6; 95% confidence interval [CI], 37.2 to 89.0), as compared with persons without these polymorphisms. A history of more than 10 pack-years of smoking has been independently associated with the development of neovascular age-related macular degeneration. Nonsmokers exposed to passive, or “secondhand,” smoke also appear to be at increased risk, and smokers may be more than twice as likely as nonsmokers to have age-related macular degeneration, after adjustment for possible confounders. Both the presence of the ARMS2 Ala69Ser variant and a history of smoking appear to synergistically confer an increased risk of the development of age-related macular degeneration, as compared with either factor alone.

Furthermore, complement factor H plasma levels are also reduced in smokers. In addition, one study reported that homozygosity for the CFH Tyr402His risk allele in smokers with more than a 10-pack-year history increases the risk of the development of age-related macular degeneration by a factor of 144. The confounders of genetic and environmental risk factors lends credence to a complex, multifactorial etiologic model of the development of age-related macular degeneration.

Other modifiable risk factors for advanced age-related macular degeneration include obesity, hypertension, high dietary intake of vegetable fat, and low dietary intake or plasma concentrations of antioxidants and zinc. Two studies have reported an increased risk of the progression of age-related macular degeneration after cataract surgery, but the Age-Related Eye Disease Study reported no association. Antioxidants have long been hypothesized to limit the damage caused by oxidative stress in the macula. In the Age-Related Eye Disease Study, which involved 3640 patients (age range, 55 to 80 years) with age-related macular degeneration, the use of a daily antioxidant supplement (PreserVision, Bausch & Lomb) consisting of vitamin C (500 mg), vitamin E (400 IU), beta carotene (15 mg), zinc oxide (80 mg), and cupric oxide (2 mg), as compared with placebo, reduced the rate of progression from intermediate to advanced age-related macular degeneration by 25% over a period of 5 years and resulted in a 19% reduction in the risk of moderate visual loss. If all Americans at risk for the development of advanced age-related macular degeneration (e.g., patients with intermediate age-related macular degeneration in one eye only) were to receive this supplementation, more than 300,000 persons (95% CI, 158,000 to 487,000) might avoid the development of advanced age-related macular degeneration during the next 5 years. However, such supplementation may not be appropriate for all patients. For example, one study showed that beta-carotene supplementation may confer a 17% increase in the relative risk of the development of lung cancer in smokers. High-dose vitamin E supplementation has been associated with an increased risk of death in a large meta-analysis and with an increased risk of heart failure (relative risk, 1.13; 95% CI, 1.01 to 1.26) among people with diabetes or cardiac disease. However, the use of the supplementation that was studied during the Age-Related Eye Disease Study was actually associated with a trend toward a reduced risk of death after an average of 6.5 years of supplementation, as compared with placebo (relative risk, 0.86; 95% CI, 0.65 to 1.12; P not significant). Ultimately, the decision to initiate supplementation according to the Age-Related Eye Disease Study should be based on a coordinated effort among the vitreo-retinal specialist, the primary care physician, and the patient.
LIFESTYLE AND DIETARY MODIFICATIONS

Given the well-described association of smoking with age-related macular degeneration, all smokers should be counseled to quit smoking. Smokers may not be aware of their increased risk for visual loss, and the possibility of legal blindness may be an important motivator for smoking cessation. Two studies have reported that people who had stopped smoking more than 20 years earlier were no longer at increased risk for age-related macular degeneration.

Patients should also be counseled to decrease dietary intake of fat, maintain healthy weight and blood pressure, and increase dietary intake of antioxidants through foods such as green leafy vegetables, whole grains, fish, and nuts. High dietary intake of beta-carotene, vitamins C and E, and zinc, as well as high dietary intake of n-3 long-chain polyunsaturated fatty acids and fish, has been independently shown to decrease the risk of the development of neovascular age-related macular degeneration. For patients with severe visual loss, low-vision devices such as electronic video magnifiers and spectacle-mounted telescopes, as well as low-vision rehabilitation services, may also be of benefit.

INTRAVITREAL ANTIANGIOGENIC THERAPY

Intravitreal antiangiogenic therapy (injection of antiangiogenic agents directly into the vitreous) is currently the primary therapy for neovascular age-related macular degeneration (Fig. 5). Intravitreal injections localize therapy to the eye, avoiding systemic administration and possibly reducing the incidence of systemic adverse effects. These procedures are generally performed in an office setting with the use of an aseptic technique and a topical or subconjunctival anesthetic. Although frequently administered during a patient’s disease course, intravitreal injections can on rare occasions cause serious adverse events such as endophthalmitis, retinal detachment, intraocular hemorrhage, increased intraocular pressure, and even anaphylaxis. The first intravitreal agent approved by the Food and Drug Administration for neovascular age-related macular degeneration was pegaptanib sodium (Macugen, OSI Pharmaceuticals), a messenger RNA aptamer and VEGF antagonist. The number of patients whose visual acuity improved with pegaptanib was limited, so the agent is no longer widely used.

RANIBIZUMAB AND BEVACIZUMAB

Currently, the most common therapies for neovascular age-related macular degeneration are intravitreal ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech). Ranibizumab is a humanized monoclonal antibody fragment that inhibits VEGF and is administered monthly. In 2006, a phase 3 trial showed that 90.0% of patients with neovascular age-related macular degeneration who were treated with 0.5 mg of ranibizumab (216 of 240 patients) had lost fewer than 15 letters (either doubling of the visual angle or three lines of visual loss on a logMAR visual-acuity chart) at a 2-year follow-up, as compared with 52.9% of control patients (126 of 238 patients). In addition, 33.3% of treated patients had their vision improved by 15 letters or more, as compared with only 3.8% of controls. Serious ocular adverse events were rare but included endophthalmitis and uveitis. Systemic adverse events, including arterial thromboembolic events and hypertension, were rare and of similar incidence in the treated and control groups. Decreasing the frequency of intravitreal ranibizumab therapy from monthly to quarterly injections appears to eliminate the improvement in visual acuity that was observed with monthly injections.

Bevacizumab, a monoclonal antibody to VEGF used intravenously as an anticancer agent, is also increasingly being used off-label as intravitreal therapy for neovascular age-related macular degeneration. Although data from long-term studies...
are not yet available, several short-term studies of intravitreal bevacizumab have shown improvement in visual acuity that is similar to the improvement with ranibizumab. Intravitreal bevacizumab appears to have systemic adverse events similar to those of ranibizumab, based on physician reports of thousands of intravitreal injections at centers throughout the world.

Since the cost per intravitreal dose of these two agents differs greatly ($1,950 for ranibizumab and approximately $30 for bevacizumab), the potentially similar efficacy of bevacizumab coupled with its dramatically lower cost may lead to an increased prevalence of its use for neovascular age-related macular degeneration. To help compare the efficacy and safety of these two agents, the National Eye Institute has initiated the Comparisons of Age-Related Macular Degeneration Treatments Trials, a multicenter, randomized clinical trial of ranibizumab and bevacizumab in the treatment of neovascular age-related macular degeneration.

Anti-VEGF agents administered systemically have been associated with serious systemic adverse events, including thromboembolic events and death. Since breakdown of the blood–ocular barrier is common in age-related macular degeneration, repeated intravitreal anti-VEGF therapy may lead to a small amount of systemic penetration of these agents and systemic VEGF inhibition, possibly resulting in serious long-term adverse events that may not yet be manifest in clinical studies.

Ocular photodynamic therapy and argon-laser photocoagulation therapy

Ocular photodynamic therapy is another method of antiangiogenic treatment, in which an intravenously administered, light-sensitive dye, verteporfin (Visudyne, Novartis), preferentially concentrates in new blood vessels and is activated with the use of a 689-nm laser beam focused over the macula, causing localized choroidal neovascular thrombosis through a nonthermal chemotoxic reaction. Although it generally does not improve vision and its use as monotherapy appears to be less efficacious than other treatments, photodynamic therapy does limit visual loss in neovascular age-related macular degeneration, and its repeated use over a period of 5 years appears to be safe, with minimal, infrequent side effects (e.g., dye extravasation at the injection site, back pain, and photosensitivity).

Argon-laser photocoagulation therapy was once the most common therapy for neovascular age-related macular degeneration. It is now used only occasionally to treat choroidal neovascularization that extends by more than 200 μm from the center of the macula, since this treatment itself can create a large retinal scar associated with permanent visual loss.

Vitreoretinal surgery

Surgical extraction of choroidal neovascularization appeared to have poor efficacy in the Submacular Surgery Trials and is now used only in very select situations. Studies of macular translocation surgery (surgical relocation of the macula) and subretinal injection of tissue plasminogen activator combined with intravitreal air injection to treat subretinal hemorrhage have shown improved visual outcomes after several months of follow-up, but data from long-term studies are lacking. Ultimately, the potential for recurrence of choroidal neovascularization and the risk of complications have relegated vitreoretinal surgery to a minor adjunct used in combination with other pharmacologic therapies for neovascular age-related macular degeneration.

Evolving approaches

As of February 2008, more than 60 phase 1 and phase 2 clinical trials are currently recruiting patients with age-related macular degeneration. The trials are assessing a wide variety of potential therapeutic agents and methods of treatment for the management of both non-neovascular and neovascular age-related macular degeneration.

The Age-Related Eye Disease Study 2 (ClinicalTrials.gov number, NCT00345176), an NIH-sponsored study initiated in early 2006, is evaluating the potential benefit of additional supplements, including the retinal carotenoids lutein and zeaxanthin, as well as n−3 long-chain polyunsaturated fatty acids, for the prevention of neovascular age-related macular degeneration.

Combination therapy

Therapy with a combination of agents is being investigated in an effort to both improve efficacy and decrease the frequency of required treat-
ments. Intravitreal injection of the corticosteroid triamcinolone acetonide (usually 4 mg) has been combined with photodynamic therapy and may result in enhanced efficacy as compared with photodynamic therapy alone.93 So-called triple therapy — the administration of an intravitreal anti-VEGF agent, intravitreal dexamethasone, and photodynamic therapy — is also currently being investigated.94

GENETIC APPROACHES
Adenoviral vector-mediated intravitreal gene transfer of pigment-epithelium–derived factor, an antiangiogenic cytokine, appears to help arrest the growth of choroidal neovascularization in humans.95 According to phase 2 studies and a phase 3 study, which began in July 2007 (ClinicalTrials.gov number, NCT00499590),96 intravitreal administration of bevacizumab, a small interfering RNA agent designed to silence VEGF RNA, appears to inhibit choroidal neovascularization. Phase 2 studies of VEGF Trap-Eye, an intravitreally administered fusion protein designed to bind VEGF, have shown improvements in visual acuity in patients who have neovascular age-related macular degeneration.97 Genetic research is also being performed to determine which patients will benefit from treatment. For example, patients homozygous for the CFH Tyr402His risk allele actually may not benefit as much from intravitreal bevacizumab therapy as do heterozygous patients.98

INTRAOCULAR DEVICES
The implantation of artificial intraocular devices might benefit patients who do not have a response to pharmacologic or gene therapy. Implantable miniature telescopes might improve the quality of life of patients with severe visual loss from end-stage age-related macular degeneration.99 Surgical implantation of optic-nerve, cortical, subretinal, and epiretinal electrically stimulated devices have all led to the perception of phosphenes (discrete, reproducible perceptions of light) in humans.100 These devices may help restore functional vision in the future but are primitive at present.

CONCLUSIONS
Age-related macular degeneration is a global disease that causes blindness, is becoming increasingly prevalent, and has no effective cure. Recent advances in clinical research have helped elucidate the pathophysiology and genetic mechanisms for the development of the disease, and new and emerging therapies have the promise to partially restore vision in patients with neovascular age-related macular degeneration. Within the next decade, we hope that continued advances in clinical research will help restore vision in patients with this severely debilitating disease and also prevent development of the disease in those at risk.

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