REVIEW ARTICLE

MEDICAL PROGRESS

Age-Related Macular Degeneration

Rama D. Jager, M.D., William F. Mieler, M.D., and Joan W. Miller, M.D.

From the Section of Ophthalmology and Visual Science, Department of Surgery, University of Chicago, Chicago (R.D.J., W.F.M.); and the Department of Ophthalmology, Harvard Medical School, Boston (J.W.M.). Address reprint requests to Dr. Jager at University Retina and Macula Associates, 6320 W. 159th St., Suite A, Oak Forest, IL 60452, or at rjager@uretina.com.

N Engl J Med 2008;358:2606-17.

Age-related macular degeneration is the leading cause of irreversible blindness in people 50 years of age or older in the developed world.[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.[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).[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.[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.[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 degen-

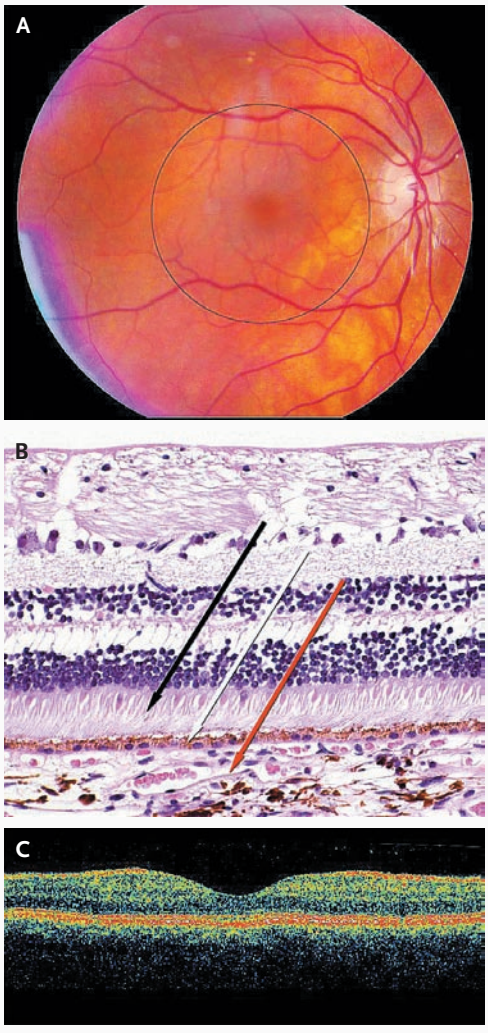

Figure 1. The Normal Retina.

Panel A is a photograph of a normal fundus and retina. The area within the black circle is the macula. Panel B shows a histologic section of normal retina, with photoreceptors (black arrow), retinal pigment epithelium (white arrow), and the choroid (red arrow). (Image courtesy of Mort Smith, M.D.) Panel C shows a cross-sectional image of the retina generated by optical coherence tomography, an imaging technique that allows for real-time, noninvasive visualization of retinal architecture.

eration, drusen are present bilaterally.[6] 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,[7] 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.[8] 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.[7,9-14]

CLASSIFICATION, CLINICAL FEATURES, AND UNTREATED DISEASE COURSE

Although multiple classification systems for age-related macular degeneration exist,[5,15,16] the classification proposed by the Age-Related Eye Disease Study, a trial sponsored by the National Institutes of Health (NIH),[17] 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 non-neovascular 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.[4,18]

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-

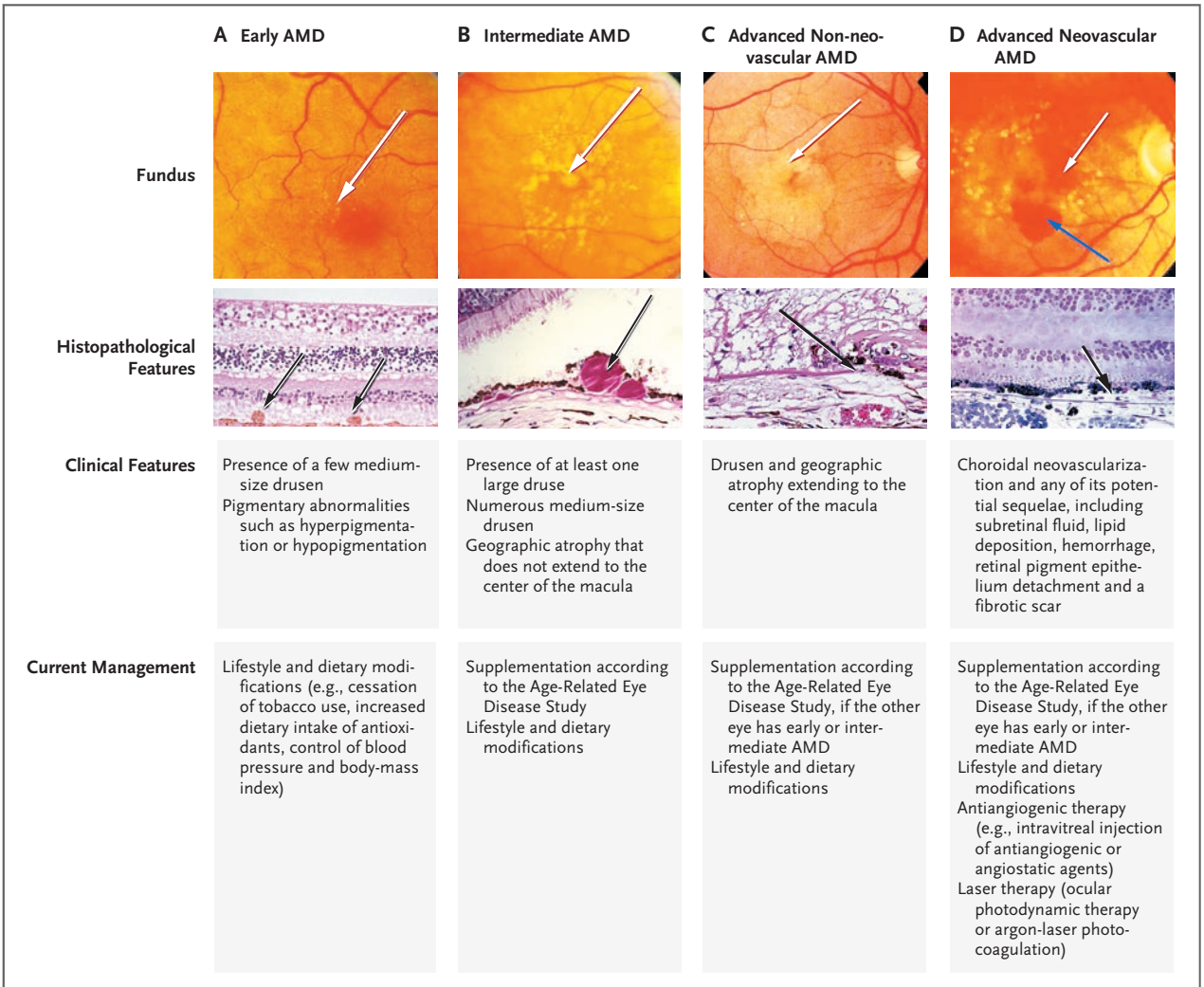

Figure 2. Classification of Age-Related Macular Degeneration (AMD).

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.)

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.[19] 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-

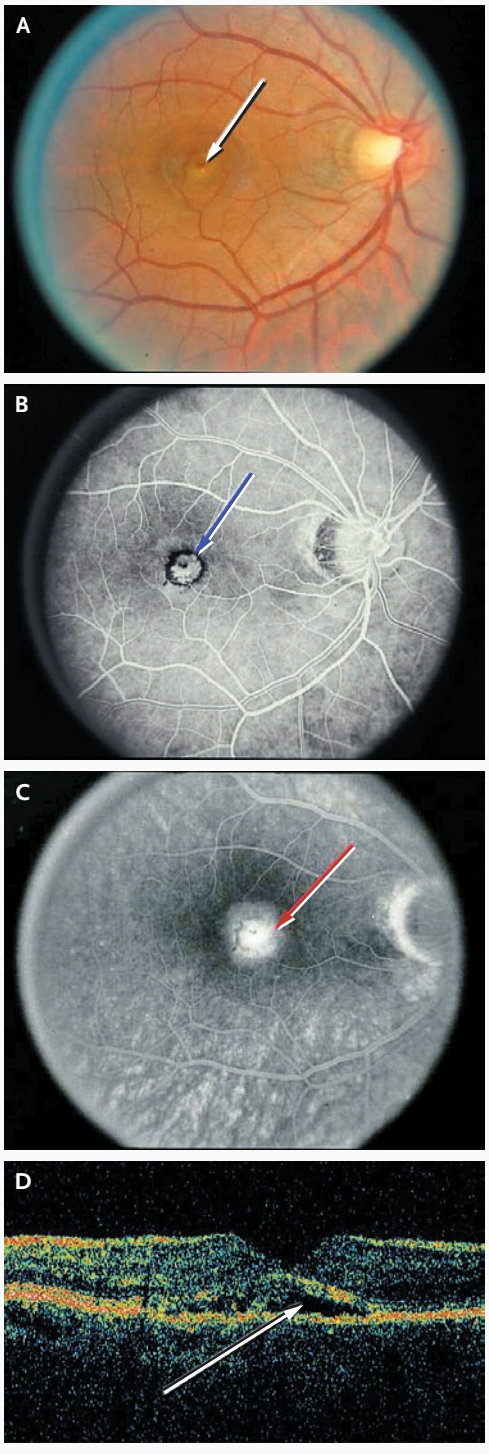

Figure 3. Imaging of Neovascular Age-Related Macular Degeneration.

Panel A shows a photograph of a fundus with neovascular age-related macular degeneration (arrow). Fluorescein angiograms show early (Panel B) and late (Panel C) frames of a patient with age-related macular degeneration and reveal early hyperfluorescence (blue arrow) and late leakage (red arrow) consistent with neovascular age-related macular degeneration and choroidal neovascularization. An optical coherence tomographic image (Panel D) reveals subretinal fluid (arrow) in an eye with neovascular age-related macular degeneration.

ness (i.e., visual acuity of 20/200 or worse) resulting from age-related macular degeneration.[20]

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.[4,21] 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.[22,23] Once advanced age-related macular degeneration develops in one eye, there is a substantial chance (43%, according to one report[24]) 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.[25]

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[26] (Table 1). Advancing age is associated with sharp rises in the incidence, prevalence, and progres-

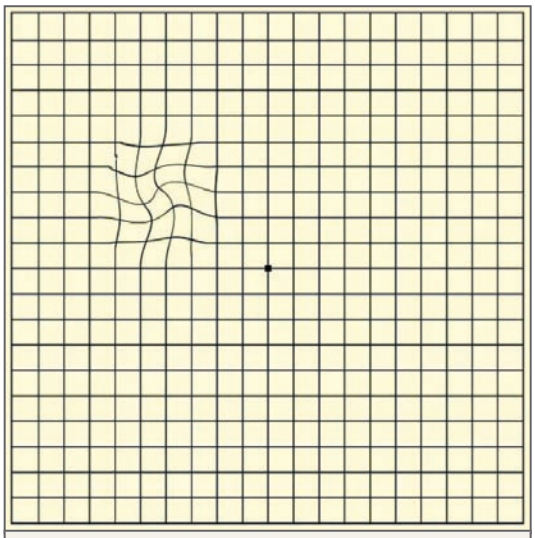

Figure 4. Amsler Grid.
The Amsler grid can be used to detect subtle areas of distortion, which can manifest as waviness of the grid lines (as shown in the upper left quadrant of the grid) as a result of neovascular age-related macular degeneration.

sion of age-related macular degeneration.[6,27-32] The estimated overall prevalence of any form of age-related macular degeneration is 9% among Americans 40 years of age or older (8.5 million affected persons).[33] The estimated prevalence of advanced age-related macular degeneration is 1.5% among Americans 40 years of age or older, with a projected 50% increase by the year 2020, primarily because of the rapidly increasing proportion of older persons in the United States.[3] The prevalence of early age-related macular degeneration has been reported to increase from 8% among people 43 to 54 years of age to 30% 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.[6] Age-related macular degeneration is more common in whites than in blacks.[34] Hispanic and Chinese persons seem to have a lower prevalence of age-related macular degeneration than whites but a higher prevalence than blacks.[35] 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.[30] Epidemiologic studies of Australian, European, and Japanese subjects have shown similar incidence and prevalence rates.[27-32]

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

Advancing age
Genetic factors
Complement factor H, Tyr402His variant
LOC387715/ARMS2, Ala69Ser variant
A history of smoking within the past 20 years
White race
Obesity
High dietary intake of vegetable fat
Low dietary intake of antioxidants and zinc

Although twin studies[36,37] and familial aggregation analyses[38] 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.[39-41] 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.[42] Other polymorphisms in *CFH* besides Tyr402His appear to increase the risk of age-related macular degeneration in Asians.[43,44] 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.[45] These studies clearly demonstrate that the

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.[46] 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.[47,48]

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.[49,50] 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.[48] Furthermore, complement factor H plasma levels are also reduced in smokers.[51] 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 neovascular age-related macular degeneration by a factor of 144.[52] The confluence 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,[25,53-57] and low dietary intake or plasma concentrations of antioxidants and zinc.[58,59] Two studies have reported an increased risk of the progression of age-related macular degeneration after cataract surgery,[60,61] but the Age-Related Eye Disease Study reported no association.[17]

CURRENT MANAGEMENT

ANTIOXIDANT SUPPLEMENTATION IN THE AGE-RELATED EYE DISEASE STUDY

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.[24] If all Americans at risk for the development of advanced age-related macular degeneration (e.g., patients with intermediate age-related macular degeneration in either eye or advanced 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.[62]

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.[63] High-dose vitamin E supplementation has been associated with an increased risk of death in a large meta-analysis[64] 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.[65] 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).[66] Ultimately, the decision to initiate supplementation according to the Age-Related Eye Disease Study should be based on a coordinated effort among the vitreoretinal 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.[67,68] 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.[50,69]

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.[58,70] 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.[71]

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.[72] 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.[73]

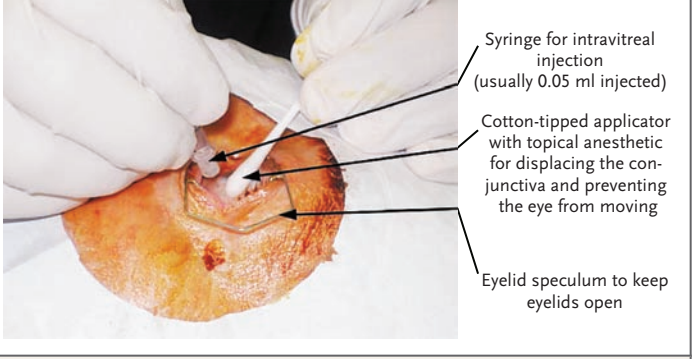

Figure 5. Intravitreal Injection.
Injection of antiangiogenic or angiostatic agents directly into the vitreous can localize therapy directly to the eye while minimizing systemic adverse effects. It is typically performed as an in-office procedure with the use of an eyelid speculum to keep the eyelids open.

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).[74] 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.[74] 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.[75]

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.[76,77] 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.[78,79]

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.[80]

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.[81]

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.[82] 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,[83] 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).[84]

Argon-laser photocoagulation therapy was once the most common therapy for neovascular age-related macular degeneration.[85] 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[86] and is now used only in very select situations. Studies of macular translocation surgery (surgical relocation of the macula)[87] 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,[88-90] 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.[91]

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.[92]

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 bevasiranib, 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.

Dr. Jager reports receiving lecture fees from Alcon, Novartis, and Genentech; Dr. Mieler, consulting fees from Genentech, speaker's fees from Alcon, and a grant from Research to Prevent Blindness; and Dr. Miller, consulting fees from Genzyme, Genentech, and Bausch and Lomb and grants from Genentech, Genzyme, and Angstrom Pharmaceutical. Dr. Miller reports that she is named on three patents from the Massachusetts Eye and Ear Infirmary related to the use of verteporfin for ocular photodynamic therapy. No other potential conflict of interest relevant to this article was reported.

We thank Anna Gabrielian, Robin Singh, and Kwesi Grant-Acquah for their assistance with the manuscript.

REFERENCES

1. Pascolini D, Mariotti SP, Pokharel GP, et al. 2002 Global update of available data on visual impairment: a compilation of population-based prevalence studies. Ophthalmic Epidemiol 2004;11:67-115.
2. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477-85.
3. Friedman DS, O'Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-72.
4. Alfaro DV, Liggett PE, Mieler WF, Quiroz-Mercado H, Jager RD, Tano Y, eds. Age-related macular degeneration: a comprehensive textbook. Philadelphia: Lippincott Williams & Wilkins, 2006.
5. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration: the International ARM Epidemiological Study Group. Surv Ophthalmol 1995;39:367-74.
6. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1992;99:933-43.
7. de Jong PT. Age-related macular degeneration. N Engl J Med 2006;355:1474-85.
8. Marneros AG, She H, Zambarakji H, et al. Endogenous endostatin inhibits choroidal neovascularization. FASEB J 2007;21:3809-18.
9. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res 2001;20:705-32.
10. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004;122:598-614.
11. Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2006;51:137-52.
12. Grossniklaus HE, Green WR. Choroidal neovascularization. Am J Ophthalmol 2004;137:496-503.
13. Anderson DH, Mullins RF, Hageman

GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134:411-31.
14. Kijlstra A, La Heij E, Hendrikse F. Immunological factors in the pathogenesis and treatment of age-related macular degeneration. Ocul Immunol Inflamm 2005;13:3-11.
15. Bressler NM, Bressler SB, West SK, Fine SL, Taylor HR. The grading and prevalence of macular degeneration in Chesapeake Bay watermen. Arch Ophthalmol 1989;107:847-52.
16. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. Ophthalmology 1991;98:1128-34.
17. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration: a case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Ophthalmology 2000;107:2224-32.
18. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium. IV. Fluorescein angiographic study of senile disciform macular degeneration. Am J Ophthalmol 1967;63:645/73-659/87.
19. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. Ophthalmology 1997;104:1677-91.
20. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984;102:1640-2.
21. Fine AM, Elman MJ, Ebert JE, Prestia PA, Starr JS, Fine SL. Earliest symptoms caused by neovascular membranes in the macula. Arch Ophthalmol 1986;104:513-4.
22. Casten RJ, Rovner BW, Tasman W. Age-related macular degeneration and depression: a review of recent research. Curr Opin Ophthalmol 2004;15:181-3.
23. Slakter JS, Stur M. Quality of life in patients with age-related macular degeneration: impact of the condition and benefits of treatment. Surv Ophthalmol 2005;50:263-73.
24. 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;119:1417-36.
25. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration: Macular Photocoagulation Study Group. Arch Ophthalmol 1997;115:741-7.
26. Klein R, Peto T, Bird A, VanNewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol 2004;137:486-95.
27. VanNewkirk MR, Nanjan MB, Wang JJ, Mitchell P, Taylor HR, McCarty CA. The prevalence of age-related maculopathy: the Visual Impairment Project. Ophthalmology 2000;107:1593-600.
28. Augood CA, Vingerling JR, de Jong PT, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). Arch Ophthalmol 2006;124:529-35.
29. Miyazaki M, Kiyohara Y, Yoshida A, Iida M, Nose Y, Ishibashi T. The 5-year incidence and risk factors for age-related maculopathy in a general Japanese population: the Hisayama Study. Invest Ophthalmol Vis Sci 2005;46:1907-10.
30. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1997;104:7-21.
31. Mukesh BN, Dimitrov PN, Leikin S, et al. Five-year incidence of age-related maculopathy: the Visual Impairment Project. Ophthalmology 2004;111:1176-82.
32. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. Ophthalmology 2002;109:1092-7.
33. Klein R, Rowland ML, Harris MI. Racial/ethnic differences in age-related maculopathy: Third National Health and Nutrition Examination Survey. Ophthalmology 1995;102:371-81. [Erratum, Ophthalmology 1995;102:1126.]
34. Bressler SB, Munoz B, Solomon SD, West SK. Racial differences in the prevalence of age-related macular degeneration: the Salisbury Eye Evaluation (SEE) Project. Arch Ophthalmol 2008;126:241-5.
35. Klein R, Klein BE, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the Multi-ethnic Study of Atherosclerosis. Ophthalmology 2006;113:373-80.
36. Seddon JM, Cote J, Page WF, Aggen SH, Neale MC. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. Arch Ophthalmol 2005;123:321-7.
37. Hammond CJ, Webster AR, Snieder H, Bird AC, Gilbert CE, Spector TD. Genetic influence on early age-related maculopathy: a twin study. Ophthalmology 2002;109:730-6.
38. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. Am J Ophthalmol 1997;123:199-206.
39. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308:385-9.
40. Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421-4.
41. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419-21.
42. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A 2005;102:7227-32.
43. Okamoto H, Umeda S, Obazawa M, et al. Complement factor H polymorphisms in Japanese population with age-related macular degeneration. Mol Vis 2006;12:156-8.
44. Chen LJ, Liu DT, Tam PO, et al. Association of complement factor H polymorphisms with exudative age-related macular degeneration. Mol Vis 2006;12:1536-42.
45. Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet 2006;38:458-62.
46. Kanda A, Chen W, Othman M, et al. A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. Proc Natl Acad Sci U S A 2007;104:16227-32.
47. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. Hum Mol Genet 2005;14:3227-36.
48. Schmidt S, Hauser MA, Scott WK, et al. Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. Am J Hum Genet 2006;78:852-64.
49. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL III. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS): AREDS report no. 19. Ophthalmology 2005;112:533-9.
50. Khan JC, Thurlby DA, Shahid H, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. Br J Ophthalmol 2006;90:75-80.
51. Esparza-Gordillo J, Soria JM, Buil A, et al. Genetic and environmental factors influencing the human factor H plasma levels. Immunogenetics 2004;56:77-82.
52. DeAngelis MM, Ji F, Kim IK, et al. Cigarette smoking, CFH, APOE, ELOVL4, and risk of neovascular age-related macular degeneration. Arch Ophthalmol 2007;125:49-54.
53. Klein BE, Klein R, Lee KE, Jensen SC. Measures of obesity and age-related eye diseases. Ophthalmic Epidemiol 2001;8:251-62.
54. Delcourt C, Michel F, Colvez A, et al. Associations of cardiovascular disease and its risk factors with age-related macular

degeneration: the POLA study. Ophthalmic Epidemiol 2001;8:237-49.
55. Schaumberg DA, Christen WG, Hankinson SE, Glynn RJ. Body mass index and the incidence of visually significant age-related maculopathy in men. Arch Ophthalmol 2001;119:1259-65.
56. Smith W, Mitchell P, Leeder SR. Dietary fat and fish intake and age-related maculopathy. Arch Ophthalmol 2000;118:401-4.
57. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch Ophthalmol 2003;121:1728-37. [Erratum, Arch Ophthalmol 2004;122:426.]
58. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 2005;294:3101-7.
59. VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 1998;148:204-14.
60. Klein R, Klein BE, Jensen SC, Cruickshanks KJ. The relationship of ocular factors to the incidence and progression of age-related maculopathy. Arch Ophthalmol 1998;116:506-13.
61. Freeman EE, Munoz B, West SK, Tielsch JM, Schein OD. Is there an association between cataract surgery and age-related macular degeneration? Data from three population-based studies. Am J Ophthalmol 2003;135:849-56.
62. Bressler NM, Bressler SB, Congdon NG, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Arch Ophthalmol 2003;121:1621-4.
63. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35.
64. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46.
65. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 2005;293:1338-47.
66. Chew EY, Clemons T. Vitamin E and the Age-Related Eye Disease Study supplementation for age-related macular degeneration. Arch Ophthalmol 2005;123:395-6.
67. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye 2005;19:935-44.
68. Bidwell G, Sahu A, Edwards R, Harrison RA, Thornton J, Kelly SP. Perceptions of blindness related to smoking: a hospital-based cross-sectional study. Eye 2005;19:945-8.
69. Evans JR, Fletcher AE, Wormald RP. 28,000 Cases of age related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking. Br J Ophthalmol 2005;89:550-3.
70. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS report no. 20. Arch Ophthalmol 2007;125:671-9.
71. Colenbrander A, Goodwin L, Fletcher DC. Vision rehabilitation and AMD. Int Ophthalmol Clin 2007;47:139-48.
72. Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreous injection: a comprehensive review. Retina 2004;24:676-98.
73. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805-16.
74. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
75. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239-48.
76. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006;26:383-90.
77. Algvere PV, Steén B, Seregard S, Kvanta A. A prospective study on intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration of different durations. Acta Ophthalmol Scand (in press).
78. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the Internet to assess drug safety worldwide. Br J Ophthalmol 2006;90:1344-9.
79. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008;246:81-7.
80. Comparison of age-related macular degeneration treatments trials: Lucentis-Avastin trial. (Accessed May 19, 2008, at http://www.clinicaltrials.gov/ct2/show/NCT00593450?term=macular+degeneration+catt&rank=1.)
81. van Wijngaarden P, Coster DJ, Williams KA. Inhibitors of ocular neovascularization: promises and potential problems. JAMA 2005;293:1509-13.
82. Gragoudas ES, Miller JW, Zografos L, eds. Photodynamic therapy of ocular diseases. Philadelphia: Lippincott Williams & Wilkins, 2004.
83. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials — TAP report. Arch Ophthalmol 1999;117:1329-45. [Erratum, Arch Ophthalmol 2000;118:488.]
84. Kaiser PK, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension: TAP report no. 8. Graefes Arch Clin Exp Ophthalmol 2006;244:1132-42.
85. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularization secondary to age-related macular degeneration: the influence of initial lesion size and initial visual acuity. Arch Ophthalmol 1994;112:480-8.
86. Hawkins BS, Bressler NM, Miskala PH, et al. Surgery for subfoveal choroidal neovascularization in age-related macular degeneration: ophthalmic findings: SST report no. 11. Ophthalmology 2004;111:1967-80.
87. Mruthyunjaya P, Stinnett SS, Toth CA. Change in visual function after macular translocation with 360 degrees retinectomy for neovascular age-related macular degeneration. Ophthalmology 2004;111:1715-24.
88. Haupert CL, McCuen BW II, Jaffe GJ, et al. Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. Am J Ophthalmol 2001;131:208-15.
89. Singh RP, Patel C, Sears JE. Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. Br J Ophthalmol 2006;90:429-31.
90. Olivier S, Chow DR, Packo KH, MacCumber MW, Awh CC. Subretinal recombinant tissue plasminogen activator injection and pneumatic displacement of thick submacular hemorrhage in age-related macular degeneration. Ophthalmology 2004;111:1201-8. [Erratum, Ophthalmology 2004;111:1640.]
91. Search results: macular degeneration | Open Studies | Phase I II. (Accessed May 19, 2008, at http://www.clinicaltrials.gov/ct2/results?term=macular+degeneration&recr=Open&phase=01&show_flds=Y&flds=X.)

92. Age-Related Eye Disease Study 2 (AREDS2). Bethesda, MD: National Eye Institute. (Accessed May 19, 2008, at http://www.nei.nih.gov/areds2/.)
93. Augustin AJ, Schmidt-Erfurth U. Verteporfin and intravitreal triamcinolone acetonide combination therapy for occult choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol 2006;141:638-45.
94. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. Retina 2007;27:133-40.
95. Campochiaro PA, Nguyen QD, Shah SM, et al. Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: results of a phase I clinical trial. Hum Gene Ther 2006;17:167-76.
96. Safety & efficacy study evaluating the Combination of Bevasiranib & Lucentis Therapy in Wet AMD (COBALT). (Accessed May 19, 2008, at http://www.clinicaltrials.gov/ct2/show/NCT00499590.)
97. Regeneron announces positive primary endpoint results from a phase 2 study of VEGF trap-eye in age-related macular degeneration. Press release of Regeneron, Tarrytown, NY, October 1, 2007. (Accessed May 19, 2008, at http://phx.corporate-ir.net/phoenix.zhtml?c=119576&p=irol-newsArticle&ID=1056960&highlight=.)
98. Brantley MA Jr, Fang AM, King JM, Tewari A, Kymes SM, Shiels A. Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to intravitreal bevacizumab. Ophthalmology 2007; 114:2168-73.
99. Hudson HL, Lane SS, Heier JS, et al. Implantable miniature telescope for the treatment of visual acuity loss resulting from end-stage age-related macular degeneration: 1-year results. Ophthalmology 2006;113:1987-2001.
100. Dowling J. Artificial human vision. Expert Rev Med Devices 2005;2:73-85.

CORRECTION

Age-Related Macular Degeneration

To the Editor: The review of age-related macular degeneration by Jager et al. (June 12 issue)[1] does not refer to an editorial accompanying the report of the Age-Related Eye Disease Study (AREDS) in the *Archives of Ophthalmology* in 2001 and two subsequent letters,[2,3,4] all of which criticized the study analysis for setting aside a negative result in which dietary supplementation with high doses of vitamins and minerals was ineffective and instead reporting on a subgroup in which the result was positive. The investigators argued that the excluded patients had too few end points to be eligible for treatment. However, the group of patients who received the supplement had greater disease progression and provided valuable data regarding early intervention.

Discarding prespecified negative analyses and reporting on positive subgroup analyses has been repeatedly discouraged.[5] The omission of the above information perpetuates the myth that the supplement used in the AREDS was effective, at the price of a treatment that has no benefit and carries undetermined risks.

Daniel Seigel, Sc.D.
1135 Pleasant Pt. Rd.
Cushing, ME 04563
dseigel@midcoast.com

References

1. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med 2008;358:2606-2617.
2. Jampol LM. Antioxidants, zinc, and age-related macular degeneration: results and recommendations. Arch Ophthalmol 2001;119:1533-1534.
3. Seigel D. AREDS investigators distort findings. Arch Ophthalmol 2002;120:100-101.
4. Ambati J, Ambati BK. Age-Related Eye Disease Study caveats. Arch Ophthalmol 2002;120:997-997.
5. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine – reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-2194.

To the Editor: The review of age-related macular degeneration contains one problem: the inaccurate use of the term ``legal blindness.´´ The authors imply that decreased vision in one eye may make that eye legally blind. This is incorrect: one eye cannot be legally blind, but a person may be legally blind. In the United States, ``Statutory blindness is defined in the law as central visual acuity of 20/200 or less in the better eye with the use of [a] correcting lens.´´[1] Additional qualifications apply in the case of restricted visual fields.[1,2] The proper definition is of financial and sociological importance to patients.

Robert J. Herm, M.D.
Robert E. Lee Ln.
Bluffton, SC 29909
b2herm@hargray.com

References

1. Social Security Administration, 20 C.F.R.§ 404.1581 (1983).
2. Tax and credits: line 39a. In: Form 1040 instructions. Internal Revenue Service, 2008:31. (Accessed September 26, 2008, at http://www.irs.gov/pub/irs-pdf/i1040gi.pdf.)

The authors reply: With regard to Seigel's comments, we believe that the authors of the report of the AREDS[1] responded adequately to any concerns raised in correspondence after publication of their article. The authors of that report recognized the potential perils of subgroup analyses of nonprespecified groups and were not issuing a blanket recommendation for megadose supplements.[2,3] Our review also acknowledges that the supplementation used in the AREDS may not be appropriate for all patients. Instead, we believe that the decision to initiate this supplementation should be based on a coordinated effort among the vitreoretinal specialist, the primary care physician, and the patient.

We disagree with the assertion that this supplementation has no benefit. In our opinion, it has clearly been shown to decrease the rate of visual loss in selected patients with age-related macular degeneration. Recommendations from the report of the AREDS are part of the evidence-based preferred practice patterns of the American Academy of Ophthalmology for the management of age-related macular degeneration, and they were rated as having the highest strength of evidence (based on study design) as well as being most important for the care process.[4]

Herm raises an important point. Indeed, one can easily infer from the article that an eye can become legally blind: ``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 blindness (i.e., visual acuity of 20/200 or worse) resulting from age-related macular degeneration.´´ The words ``or legal blindness´´ should have been omitted from the article. Herm is correct, and his point is well taken.

Rama D. Jager, M.D.
University of Chicago
Chicago, IL 60637
rjager@uretina.com

William F. Mieler, M.D.
University of Illinois
Chicago, IL 60612

Joan W. Miller, M.D.
Harvard University
Boston, MA 02115

References

1. 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;119:1417-1436.
2. Seigel D. AREDS investigators distort findings. Arch Ophthalmol 2002;120:100-101.
3. Ambati J, Ambati BK. Age-Related Eye Disease Study caveats. Arch Ophthalmol 2002;120:997-997.
4. The Ophthalmic News & Education Network, American Academy of Ophthalmology. Age-related macular degeneration. (Accessed September 26, 2008, at http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=0e2b5946-d493-4a4a-80fa-6f40841b1405#section5.)