A 76-Year-Old Man With Macular Degeneration

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DR SHIP: Dr G is a 76-year-old semiretired surgeon. He is married, lives in the New York metropolitan area, and has indemnity insurance and Medicare.

Dr G’s ophthalmologic history was notable for mild myopia, bilateral drusen, and an episode of self-limited central serous retinopathy in the left eye at the age of 38 years. Approximately 3 years ago, he noted subtle vision changes. These symptoms progressed over a 2-month period and he saw his general ophthalmologist. He was found to have mild nuclear sclerotic cataracts (right greater than left), corrected visual acuity of 20/40 in the right eye and 20/25 in the left eye, and an exudative retinal detachment in the right eye. He was referred to a retinal specialist that day.

Since that time, Dr G has received photodynamic therapy (PDT) to the right eye 5 times, twice with the experimental addition of intraocular triamcinolone. His visual acuity in the right eye initially showed some interval improvement, but has ultimately worsened to “count fingers” vision. His course has been complicated by chronic dry eyes, for which he has been unsuccessfully treated with artificial tears and cyclosporine drops, as well as bilateral nuclear sclerotic cataracts. Cataract surgery for the left eye was aborted 3 months ago when he sustained an intraorbital hemorrhage during anesthesia that required treatment by lateral canthotomy.

Dr G’s loss of visual acuity has dramatically altered his life. While he continues to teach, he stopped performing surgery when he lost depth perception (stereopsis) because of changes in the right eye. He does not feel he has adequate binocular vision to drive safely, so has become reliant on family, friends, and public transportation with the attendant loss of autonomy. He finds variable but occasionally profound difficulty seeing well enough to do small household repairs, to play the piano, and to read, all activities that used to occupy his time. He has become depressed.

Dr G’s past medical history is significant for hypertension, osteopenia, mild anemia, and migraine. Fifteen years ago his purified protein derivative test converted to positive and he took a course of isoniazid. His surgical history is notable for a prostatectomy and thymectomy.

His current medications include the following: alendronate (35 mg every week), hydrochlorothiazide (12.5 mg daily), amlodipine (10 mg daily), aspirin (80 mg every other day), as well as naproxen and misoprostol (200 µg as needed for migraine). He has no drug allergies. He has a remote history of pipe smoking and drinks alcohol socially.

At his most recent ophthalmologic examination, his visual acuity in the right eye was 20/400, in the left eye 20/30. The left fundus showed large soft drusen larger than 125 µm, mild pigmentary mottling, but no evidence of subretinal fluid or hemorrhage.

Dr G wonders what he can do to avoid developing similar sight-threatening changes in his left eye and asks if there are any other treatments for his right eye that he might consider.

DR G: HIS VIEW

It was during the summer about 3 years ago. I became aware, while I was driving, of a subtle change in the shape of billboards. The upper right hand corner of the billboard appeared to be sagging. And then I noticed that if I looked at a page, the upper right hand corner of the page would sag. And I thought this was most unusual.

My ophthalmologist could not find anything on her examination, so she referred me to a retina specialist. I’ve received 4 treatments, but I’ve had a substantial loss of vision.

The vision changed in spurts. It wasn’t a subtle progression at all. I kept going in to have my prescription changed. I must have gone through two dozen pairs of glasses in the last 3 years.

See also Patient Page.

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The issue that bothers me most is that I can no longer work as a surgeon, I can no longer operate. Losing depth perception has been the most significant thing. It’s been absolutely devastating. My eye-hand coordination was my life. In the operating room, I can’t demonstrate a procedure. It’s astoundingly defeating.

I want to protect the vision in my good eye. I’ve always been a therapeutic nihilist. I never believed that multivitamins and all these extra things are necessary. But I take zinc and lutein because it isn’t going to do any harm. And maybe it might help to forestall the development of macular degeneration in the good eye.

I would like to know what else I can do to protect the vision in that eye and I’d like to do everything I can so that I can read with greater ease. Because not being able to read, not being able to write, not able to drive, and not being able to function with fluidity is a terrible handicap.

QUESTIONS FOR DR ARROYO

What is the epidemiology and pathophysiology of the 2 major types of macular degeneration? What are the risk factors, how do patients typically present, and how is the diagnosis made? What is the natural history of age-related macular degeneration (AMD)? What treatments exist? What are their complications, if any? What can be done to prevent AMD in those at risk and/or to delay progression? What does the future hold? What do you recommend for our patient?

DR ARROYO: As Dr G’s case helps illustrate, AMD is the leading cause of irreversible vision loss in patients older than 55 years. As it did for Dr G, AMD often presents with acute, unilateral central visual distortion and loss. Early diagnosis and treatment of AMD provide the best chance of maintaining vision, quality of life, and overall health of the patient. New treatment options are on the horizon that promise to improve vision, as opposed to simply reduce the rate of vision loss. Attention and resources need to be directed toward understanding the pathophysiology underlying non-neovascular or dry AMD and formulating effective treatments that prevent severe vision loss from geographic atrophy and choroidal neovascularization (CNV).

Overview of Macular Degeneration

Age-related macular degeneration is a degenerative disease of the macula (FIGURE 1) that is characterized by the focal accumulation of yellowish material under the retinal pigment epithelium (RPE) (called drusen) and RPE pigmentedary changes in the early stages, and geographic atrophy and CNV in the advanced stages of the disease. Drusen range from small, well-defined hard drusen (FIGURE 2), large, ill-defined, soft drusen (Figure 2), or crystalline, calcific drusen (Figure 2). The risk of progression to advanced AMD is 0.5% to 50% over 5 years and increases as the size and number of drusen increase (>125 µm in either eye or >63 µm in both eyes) and with the presence of RPE pigmentary disturbances.

Progression to advanced AMD is usually associated with severe vision loss due to geographic atrophy of the fovea in 20% of cases (FIGURE 3) or CNV in 80% of cases. Neovascular or wet AMD is characterized primarily by growth of abnormal vessels from the CNV into the sub-RPE and/or subretinal space. Less frequently, these abnormal vessels may originate from the retinal circulation. Choroidal neovascular vessels leak, leading to localized exudative retinal detachment and/or bleeding underneath the retina.

Pathophysiology of AMD

Although the exact pathogenesis of non-neovascular AMD is unknown, a number of theories have been proposed: (1) photoreceptor and RPE ischemia and/or decreased diffusion through Bruch membrane; (2) primary senescence of the RPE; (3) primary genetic abnormalities in the photoreceptor or RPE; and (4) decreased scleral elasticity. The development of drusen may be a final common pathway that results from any of the above-mentioned etiologies or may be multifactorial in nature. Factors such as inflammation and chronic infection may also play a role in this disease. The ability to develop effective treatments for non-neovascular dry AMD is hampered by our limited understanding of its pathophysiology.

In contrast, the molecular events driving neovascularization are much better understood. This insight has allowed the development of effective antineovascular treatments that target different molecular events involved in neovascular AMD.

Risk Factors for AMD

Age-related macular degeneration is associated with certain risk factors that may provide insight into its origins as well as allow for risk modification. These factors include age, family history, race, smoking, hypertension, atherosclerosis, inflammation, obesity, consumption of food high in antioxidants, fish and nuts, and chronic infection.

Age is the most strongly associated risk factor for AMD. Prevalence data are available from a study of 14,752 people aged 43 to 99 years, which pooled the results of 3 studies from the United States, the Netherlands, and Australia. Wet or dry type AMD was found in 1.6% of all people, but in no one younger than 55 years. Between the ages of 55 and 64 years, 65 and 74 years, 75 and 84 years, and after age 84 years, the rates were 0.2%, 0.9%, 4.6%, and 13.1%, respectively. It is estimated that in 2000 the prevalence of AMD in US adults aged 40 years and older was 1.47%, affecting 1.75 million people, and by 2020 will affect almost 3 million people as the US population ages. Smoking is also strongly associated with an increased risk of dry and wet type AMD, with relative risks (RRs) ranging from 2 to 4 compared with individuals who never smoked.
The macula is the central part of the retina delimited by the superior temporal and inferior temporal retinal vascular arcades. The fovea is about the size of the optic nerve (diameter, 1500 µm) and is centered on the foveola (diameter, 350 µm). The foveola is the thinnest part of the retina. It is devoid of ganglion cells and is responsible for the most acute detailed vision. A photon of light must penetrate all of the layers of the retina before being absorbed and converted into a neural signal by the photoreceptor outer segments. This retinal transparency results from the structured organization and orientation of the retinal cell bodies and processes. The retinal photoreceptors and retinal pigment epithelium (RPE) are metabolically active cells that depend on the choroidal vasculature to supply oxygen and nutrients and remove metabolic waste.

Dry AMD or nonneovascular AMD is characterized by nodular, hard drusen, with sharp edges, diffuse soft drusen, and RPE hyperplasia and hyperpigmentation. Histologically, drusenoid material is found between the RPE and the RPE basement membrane (basal laminar deposits) and/or between the RPE basement membrane and the collagenous layer of Bruch membrane (basal linear deposits). The risk for progression to wet or neovascular AMD increases with increasing number and size of drusen and the presence of RPE pigmentary abnormalities.

Wet AMD or neovascular AMD is characterized by the intrusion of abnormal new vessels from the choroid into the subretinal (type 2) and/or sub-RPE (type 1) space. In some cases, neovascularization may originate from the retinal vessels (not shown), with or without a choroidal component. Choroidal neovascularization often exudes fluid and/or hemorrhage into the subretinal and/or sub-RPE space.
The increased risk of AMD is consistently seen in most studies and may persist even after quitting smoking for 15 to 20 years.32,50

Family history is associated with AMD,29 although the association may be stronger in patients with early onset disease.51 Four recent studies have found that a tyrosine-histidine single protein polymorphism within the AMD locus of chromosome 1 that is responsible for heparin and C-reactive protein binding is found in up to 50% cases of AMD.17-20 This protein polymorphism is thought to regulate the alternative complement pathway and result in increased inflammation. Other investigators have demonstrated that C-reactive protein is elevated in patients with AMD.21,22 Data on aspirin use and incident AMD is conflicting, although it may decrease the risk of neovascular AMD.52-54 Calcium channel blockers may be associated with

Figure 2. Types of Drusen in Age-Related Macular Degeneration (AMD)

A, Hard drusen are small, well-defined, homogeneous, yellowish deposits (also known as basal laminar deposits) found under the macula or retinal periphery. These small lesions (<63 µm) are not associated with an increased risk of AMD. B, Soft drusen are medium and large, heterogeneous, yellowish deposits with ill-defined borders that are associated with AMD. They may result in a focal elevation of the retinal pigment epithelium (RPE) called a pigment epithelial detachment. Note the subtle RPE mottling near the fovea. The presence of medium-size drusen (>63 µm) in both eyes or large drusen (>125 µm) in one or both eyes and/or pigmented disturbance (hyperpigmentation or hypopigmentation) in one or both eyes is associated with an increasing risk of advanced AMD and severe vision loss: 0.5% (no risk factors), 3% (1 risk factor), 12% (2 risk factors), 25% (3 risk factors), and 50% (4 risk factors) over a 5-year period.1 C, Calcific drusen are crystalline, refractile, subretinal yellowish lesions that may appear late in AMD. These lesions are typically associated with an increased risk of progression to advanced AMD.

Figure 3. Geographic Atrophy of the Retinal Pigment Epithelium (GARPE), Neovascular or Wet Age-Related Macular Degeneration (AMD), and Classic Subretinal Choroidal Neovascularization

A, Geographic atrophy of the retina and underlying RPE associated with AMD. Involvement of the center of the fovea by GARPE constitutes advanced AMD and typically is associated with severe vision loss. B, Neovascular or wet AMD with subretinal fluid and hemorrhage in the macula of a patient with sudden visual distortion and loss. These findings are typically due to a choroidal neovascular membrane leaking fluid (subretinal fluid) and bleeding (subretinal hemorrhage) under the retina. C, Fluorescein angiogram showing classic subretinal choroidal neovascularization. Fluorescein dye is injected in the antecubital vein, enters the retinal and choroidal circulation, and is imaged using a high-resolution fundus camera. Subretinal lesions that hyperfluoresce early in the angiogram and leak late in the angiogram as seen in this image are consistent with choroidal neovascularization, which is the sine qua non of neovascular AMD.
an increased incidence of AMD, although the evidence is not very strong.55 Finally, *Chlamydia pneumoniae* may be a possible infectious trigger of inflammation associated with AMD; however, serological and pathological data are contradictory.26,45-48

Hypertension, level of elevated blood pressure, and increased pulse pressure are also associated with AMD.44-48 Thermal laser photocoagulation appears to be less successful in patients with hypertension,57 and hypertension may increase the risk of developing AMD in the second eye among those who have one eye affected by the disease.56

A number of epidemiological studies have suggested a protective effect of consuming foods rich in carotenoids, particularly dark green leafy vegetables, and fruit.41,42 A recent study of 560 participants followed up for a mean of 8 years found that high dietary intake of beta carotene, vitamins C and E, and zinc was associated with a 35% reduced risk of progression of AMD, although this risk appears to decrease with consumption of fish and nuts.53,54 Obesity may also be associated with progression to advanced AMD.58

All individuals who have a diagnosis of AMD or a family history of AMD should be informed of the definite association of AMD with smoking and family history, the probable association with obesity, hypertension, hyperlipidemia, and cataract surgery, and the possible association with sun exposure, and may benefit from risk factor modification. Increasing consumption of foods that are rich in vitamin E and C, beta carotene, and zinc, as well as fish (high in omega-3 fatty acids) and nuts, although not proven to be effective in a prospective randomized controlled trial (RCT), is also probably beneficial.

**Natural History of AMD**

As with Dr G’s right eye, distortion of straight lines is one of the earliest symptoms associated with neovascular or wet AMD (Figure 4).37 In the primary care setting, a complaint of visual disturbance should prompt questions regarding the rate of vision loss, whether one or both eyes are involved, and whether the vision loss is for distance vision, near vision, or both. Unilateral vision loss that has occurred acutely over a period of days or weeks may represent an urgent condition and requires ophthalmologic evaluation within 24 to 48 hours.

Patients with acute distortion or loss of central vision require a dilated fundus examination. The macula is easily visualized using slit-lamp biomicroscopy. The presence of subretinal fluid associated with exudative retinal detachment, subretinal hemorrhage, or a gray subretinal membrane are all strongly suggestive of a CNV (Figure 3). A fluorescein angiogram is needed to precisely delineate the location and type of CNV present (Figure 3).

**Treatment Options for AMD**

**Antioxidants.** Antioxidants have been proposed to prevent cellular damage in the RPE by limiting the damaging effects of free radicals produced in the process of light absorption.58 The Age-Related Eye Disease Study (AREDS) studied 3640 patients aged 55 to 80 years who were randomly assigned to 1 of 4 treatment groups: (1) antioxidants (500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta carotene); (2) 80 mg of zinc as zinc oxide and 2 mg of cupric oxide (copper); (3) antioxidants plus zinc; or (4) placebo. During an average follow-up of 6.3 years, the following findings were reported: patients with no AMD (category 1) or mild or borderline AMD (category 2) did not benefit from antioxidant and/or zinc supplementation. Patients with moderate and advanced AMD (categories 3 and 4) had a lower risk of progression to advanced AMD and visual acuity loss in the good eye if they took both zinc and antioxidants compared with placebo for 7 years (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). Therefore, patients with extensive intermediate-size drusen, at least 1 large druse, or noncentral geographic atrophy in one or both eyes benefited from this treatment combination.59 In patients who were at the highest risk for AMD progression, both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD (antioxidants plus zinc: OR, 0.66
[99% CI, 0.47-0.91]; absolute risk reduction [ARR] in the proportion of eyes developing advanced AMD in 5 years, 0.06; number needed to treat [NNT] to prevent 1 case of progression to advanced AMD, 17; zinc: OR, 0.71 [99% CI, 0.52-0.99]; ARR, 0.036, NNT = 27; antioxidants: OR, 0.76 [99% CI, 0.55-1.05]). It is estimated that if all individuals in the United States who are at high risk for developing advanced AMD used the recommended antioxidant and zinc supplementation, approximately 300,000 of these individuals would avoid developing severe vision loss during the next 5 years.60

Based on the results of this RCT, to detect potentially treatable disease, all individuals older than 55 years should have a dilated fundus examination of both eyes to determine if they have signs of moderate AMD. Individuals who have extensive intermediate-size drusen, at least 1 large druse or noncentral geographic atrophy in one or both eyes, should consider treatment with vitamin A, C, and beta carotene, plus zinc.

However, patients should be aware that beta-carotene supplementation has been linked to an increased risk of lung cancer in patients who smoke.61 Two large chemoprevention trials (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study [ATBC] and Beta-Carotene and Retinal Efficacy Trial [CARET]) found an excess incidence of lung cancer and overall mortality in patients who smoked and were taking high doses of beta carotene.62,63 The relative increase in lung cancer incidence was 17% within the first 3 years following study termination in the ATBC trial (absolute risk increase, 0.00084 lung cancer cases per person-year; number needed to harm to produce 1 case of lung cancer, 1,190) and 12% in the first 6 years following study termination in the CARET trial (absolute risk increase, 0.0033 lung cancer cases per person-year; number needed to harm, 294). Given these findings and the fact that zinc alone was found to have a beneficial effect (although less pronounced) in patients who were at high risk of AMD progression, it seems prudent not to recommend beta carotene treatment in smokers.

High doses of vitamin E (≥400 IU/d) in patients with heart disease or diabetes was associated with a significant increase in the rate of heart failure (RR, 1.13 [95% CI, 1.01-1.26]; P = .03) in the Heart Outcomes Prevention Evaluation (HOPE) trial.64 A large meta-analysis of 135,967 participants in 19 clinical trials of vitamin E found that the pooled all-cause mortality risk difference in high-dose (≥400 IU) vitamin E trials was 39 per 10,000 persons (95% CI, 3.74 per 10,000 persons; P = .035).65 The proven risk reduction in AMD progression and vision loss derived from taking high-dose antioxidants plus zinc needs to be weighed against the increased risk of heart failure and all-cause mortality associated with high-dose vitamin E.

**Laser Treatment.** Thermal laser photocoagulation uses high-intensity thermal laser energy to cause coagulation of the CNV and localized damage to the overlying retina. It is an outpatient procedure that requires only topical anesthetic drops. Several large RCTs found that thermal laser photocoagulation of well-defined extrafoveal CNV associated with AMD reduced the RR of severe visual loss (loss of ≥6 lines of vision or a quadrupling of the visual angle) over 5 years.66-68 Specifically, at 5 years of follow-up, 47% of treated eyes vs 65% of control (untreated) eyes experienced severe vision loss. Unfortunately, CNV typically recurs within 2 years in approximately one half of patients treated. Thermal laser photocoagulation is restricted to use in patients with well-defined CNV, which is present in only 15% of patients who develop wet AMD. The CNV in Dr G’s right eye was subfoveal at presentation and thus would not have been eligible for thermal laser treatment.

Photodynamic therapy involves intravenous injection of a photosensitive dye such as verteporfin 5 minutes prior to application of a cool photocoagulating laser.73,74 Animal studies have shown that the wavelength, intensity, and duration of treatment used do not appreciably affect the retina, but instead activate the verteporfin that is preferentially adsorbed to the CNV.75,76 The activated dye forms reactive free radicals that damage vascular endothelium, which results in thrombosis of the damaged vessels. However, with time, some of these vessels may reopen, requiring retreatment. Photodynamic therapy does not usually restore good vision.

As in Dr G’s case, PDT is indicated for patients who have a subfoveal CNV. The efficacy of this approach has been demonstrated in placebo-controlled RCTs. In an analysis of 2 such trials including 609 patients, PDT was associated with a significant benefit in visual acuity at 1-year follow-up compared with placebo.77 Compared with baseline, 246 (61%) of 402 eyes assigned to receive PDT vs 96 (46%) of 207 eyes assigned to receive placebo had lost fewer than 15 letters of visual acuity (doubling of the visual angle or a 3-line loss of vision on a logMAR visual acuity chart). In subgroup analysis, this benefit was limited to patients with predominantly classic CNV (well-defined lesions that hyperfluoresce early and leak late on the fluorescein angiogram). Open-label follow-up of this cohort for up to 3 years found that vision outcomes remained relatively stable and that PDT could be safely repeated.78

Another trial that extended follow-up to 2 years noted similar benefits of PDT compared with placebo.80 In this study, however, benefits also extended to CNV that was less than 50% classic or 100% occult. Subgroup analyses of 100% occult lesions with no classic CNV at baseline demonstrated a greater treatment benefit in cases with either smaller lesions (<4 disc areas) or lower levels of visual acuity (20/50 or worse) at baseline. Patients received on average 3 treatments in the first year and 5 treatments over 2 years of follow-up.

Thermal laser treatment directed toward an extrafoveal choroidal feeder vessel supplying a CNV has been proposed. These studies require specialized high-speed fluorescein and indocyanine green scanning laser angiography.
to accurately identify potentially treatable CNV feeder vessels.
Further results are needed prior to making treatment recommendations.

**Pharmacological Treatment.** Vascular endothelial growth factor (VEGF) is a potent endothelial mitogen and vascular permeability factor that plays a pivotal role in neovascularization.

Antagonists to this important growth factor may help mitigate the growth and permeability of CNV.
A number of VEGF inhibitors have been developed and are under investigation.
These agents are typically injected in the eye every 4 to 6 weeks.

Two concurrent phase 3 trials of the VEGF antagonist pegaptanib have been published.
A total of 1186 patients with wet AMD were treated with 3 doses of intravitreal pegaptanib or placebo.
Overall, patients who received intravitreal pegaptanib injection every 6 weeks lost less than 3 or more lines of visual acuity vs control patients (70% treated; 55% controls; P<.001).
Adverse effects included endophthalmitis (1.3% per year), traumatic cataract (0.7%), and retinal detachment (0.6%).
Pegaptanib is the first anti-VEGF drug for the treatment of neovascular AMD approved by the US Food and Drug Administration (FDA).

Vascular endothelial growth factor antagonists block neovascularization, an end-stage event in the overall pathophysiology of AMD.
Anti-VEGF therapy may need to be continued indefinitely to treat recurrent neovascularization.
The long-term complications associated with chronic VEGF inhibition in the eye are unknown.

**Surgical Treatment.** Two surgical procedures are under investigation: submacular surgery and macular translocation surgery.
Submacular surgery involves the removal of abnormal subretinal neovascularization and, if present, large submacular hemorrhages.
Macular translocation surgery involves surgically detaching the fovea and moving it from a more diseased area of RPE to a less diseased area.

The Submacular Surgery Trials studied submacular surgery for subfoveal CNV associated with AMD.
These investigators found that submacular surgery for new subfoveal lesions with less than 50% blood did not improve or preserve visual acuity for 24 months in more eyes (41%) than observation (44%) and is not recommended for patients with wet AMD.
In addition, submacular surgery for group B lesions (>50% blood) did not increase the chance of stable or improved (≥2 lines of vision) visual acuity (56% in the surgery group vs 59% in the observation group) and was associated with a high risk of rhegmatogenous retinal detachment (16% in the surgery group vs 2% in the control group).
However, it did reduce the risk of severe visual acuity loss (loss of ≥6 lines of vision) compared with observation (21% vs 36%, P = .004).

Macular translocation is a complicated surgical procedure that relocates the fovea on healthier RPE and has the potential of preserving foveal photoreceptor function.
Results from recent case series with macular translocation surgery are encouraging, but no RCT has been performed.

These consecutive, noncomparative case series of 15 to 90 patients followed for at least 1 year demonstrated an overall improvement in vision in 0% to 66%, and loss of vision in 6% to 32% of patients.
The most recent of these case series of 64 patients demonstrated an improvement of median distance vision from 20/125 before surgery to 20/80 at 1 year (P = .03) and median reading speed of 71 to 105 words per minute (P<.001).
Eleven percent of patients had a greater than 3-line loss of vision, and 13% of patients ended up with less than 20/200 vision; both are consistent with the natural history of wet AMD.
The learning curve for acquiring the skills needed to perform this surgery is substantial and has thus limited the number of surgeons who perform it.
Due to the complexity and risks associated with this surgery, 360° macular translocation surgery is only considered in patients whose disease is unresponsive to other treatment or who are ineligible (eg, having large submacular hemorrhages) for nonsurgical treatment.

None of the currently available AMD treatments, except perhaps 360° macular translocation, has been shown to improve average visual acuity.

**Future Treatment Options for AMD**

**AMD Prevention.** The primary objective of the AREDS II chemoprevention trial is to evaluate the effect of antioxidants (10 mg/d lutein and 2 mg/d zeaxanthin with or without 1 g/d of omega-3 long-chain polyunsaturated fatty acids) on the progression to advanced AMD.
The secondary objective is to establish the effects of these supplements on moderate vision loss and to study the effects of eliminating beta carotene and reducing zinc in the original AREDS formulation (Table).

Anecortave acetate is a steroid derivative that has antiangiogenic properties, but lacks glucocorticoid activity.
This drug is administered in a peribulbar fashion using a special cannula and lasts approximately 6 months.
Initial studies of this drug and technique suggest a good safety profile.
A large preventive clinical trial is currently under way to evaluate whether peribulbar anecortave acetate can decrease the risk of progression from dry to wet AMD.

Therapeutic apheresis is an extracorporeal blood purification method that is being studied in patients with dry AMD.
The proposed mechanism of action of this technique is that removal of high-molecular-weight proteins and lipids reduces plasma viscosity and enhances endothelial cell function, which leads to improvement of choroidal perfusion.
A double-masked RCT (the Multicenter Investigation of Rhoferesis for AMD [MIRA-1]) of double filtration plasmapheresis or rhesopheresis in patients with dry AMD is currently under way and enrolling patients.

Interim results for 43 patients with 1 year of follow-up revealed a greater than 3-line improvement in vision (16% vs 0%) and reduced vision loss of 3 or more lines (4% vs 16%) in rhesopheresis vs control subjects, respectively.
Although the initial results look promising, further work is needed to clarify
the precise benefits and risks associated with this expensive and complicated treatment.102

Finally, drusen have been shown to spontaneously disappear and reappear in up to 30% of patients with dry AMD121 and have been noted to disappear soon after thermal laser photocoagulation treatment.122 The reasons for the disappearance of drusen are unknown. Investigators have hypothesized that laser-induced regression of high-risk drusen may reduce the risk of developing advanced AMD. Unfortunately, initial results from the Choroidal Neovascularization Prevention Trial (CNVPT) demonstrated that eyes receiving prophylactic scatter laser treatment were more likely to develop neovascularization than were control eyes.103-106 Final results from the CNVPT and the Complications of Age-related Macular Degeneration Prevention Trials (CAPT)107 are needed to clarify the exact benefits and risks of this procedure.

Laser Treatment. Rostaporfin is a photoactive drug that is being used with PDT in patients with neovascular AMD in studies outside the United States. Transpupillary thermotherapy does not appear to provide a significant benefit to patients with neovascular AMD.

Pharmacological Treatment. Future pharmacological treatments for wet AMD are directed at different sites in the mo-

<table>
<thead>
<tr>
<th>Study and Related References</th>
<th>Treatment</th>
<th>Design</th>
<th>Inclusion</th>
<th>Outcome</th>
<th>Stage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS II14</td>
<td>Lutein/zeaxanthin ± omega-3 fatty acids</td>
<td>RCT</td>
<td>AMD Prevention Trials</td>
<td>Moderate AMD</td>
<td>Progression to advanced AMD</td>
<td>Enrollment</td>
</tr>
<tr>
<td>Retaine risk reduction17,18</td>
<td>Peribulbar anecortave acetate</td>
<td>RCT</td>
<td>Moderate AMD</td>
<td>Progression</td>
<td>Follow-up</td>
<td>N = 2500</td>
</tr>
<tr>
<td>Rheopheresis19-102</td>
<td>Blood apheresis</td>
<td>RCT</td>
<td>Moderate AMD</td>
<td>Progression Visual acuity</td>
<td>Analysis</td>
<td>N = 180; preliminary findings nonsignificant</td>
</tr>
<tr>
<td>CNVPT100-106</td>
<td>Laser to drusen</td>
<td>RCT</td>
<td>Moderate AMD</td>
<td>Progression</td>
<td>Analysis</td>
<td>Nonsignificant findings</td>
</tr>
<tr>
<td>CAPT107</td>
<td>Laser to drusen</td>
<td>RCT</td>
<td>Moderate AMD</td>
<td>Progression</td>
<td>Analysis</td>
<td>Nonsignificant findings</td>
</tr>
<tr>
<td>Photrex106</td>
<td>Rostaporfin PDT</td>
<td>RCT</td>
<td>CNVM</td>
<td>Visual acuity</td>
<td>Recruitment</td>
<td>N = 660; outside United States</td>
</tr>
<tr>
<td>TTT4CNV102,110</td>
<td>Transpupillary thermotherapy</td>
<td>RCT</td>
<td>CNVM</td>
<td>Visual acuity</td>
<td>Analysis</td>
<td>N = 305; nonsignificant findings</td>
</tr>
<tr>
<td>Pharmacological Treatment Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANCHOR111</td>
<td>Ranibizumab vs verteporfin PDT</td>
<td>RCT</td>
<td>Predominantly classic CNVM</td>
<td>Maintained or improved visual acuity</td>
<td>Follow-up</td>
<td>N = 423; significant difference at 1 y</td>
</tr>
<tr>
<td>MARINA112</td>
<td>Ranibizumab every mo × 24</td>
<td>RCT</td>
<td>Minimally classic/occult CNVM</td>
<td>Maintained or improved visual acuity</td>
<td>Follow-up</td>
<td>N = 716; significant difference at 1 y</td>
</tr>
<tr>
<td>FOCUS113</td>
<td>Verteporfin PDT ± ranibizumab</td>
<td>RCT</td>
<td>Predominantly classic CNVM</td>
<td>Maintained or improved visual acuity</td>
<td>Follow-up</td>
<td>N = 162; significant difference at 1 y</td>
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<td>SAILOR114</td>
<td>Ranibizumab every mo × 3 then as needed</td>
<td>RCT</td>
<td>New or previously treated CNVM</td>
<td>Safety; moderate visual acuity loss, time to retreatment</td>
<td>Enrolling</td>
<td>N = 5000</td>
</tr>
<tr>
<td>PIER111</td>
<td>Ranibizumab every mo × 3 then every 3 mo × 6</td>
<td>RCT</td>
<td>Any CNVM</td>
<td>Maintained or improved visual acuity</td>
<td>Follow-up</td>
<td>N = 184</td>
</tr>
<tr>
<td>siRNA115,116</td>
<td>Cand5</td>
<td>RCT</td>
<td>CNVM</td>
<td>Maintained visual acuity</td>
<td>Follow-up</td>
<td>N = 120</td>
</tr>
<tr>
<td>PEDF117,118</td>
<td>Ad PEDF</td>
<td>Open-label</td>
<td>CNVM</td>
<td>Safety</td>
<td>Complete</td>
<td>N = 20</td>
</tr>
<tr>
<td>Retaine119</td>
<td>Anecortave acetate vs PDT</td>
<td>RCT</td>
<td>CNVM</td>
<td>Maintained visual acuity</td>
<td>Complete</td>
<td>N = 511</td>
</tr>
<tr>
<td>Retaine119</td>
<td>Anecortave acetate every 3 mo vs every 6 mo</td>
<td>RCT</td>
<td>CNVM</td>
<td>Maintained visual acuity</td>
<td>Enrolling</td>
<td>N = 288</td>
</tr>
<tr>
<td>Squalamine PK120</td>
<td>Intravenous squalamine</td>
<td>RCT</td>
<td>CNVM</td>
<td>Maintained visual acuity</td>
<td>Enrolling</td>
<td>N = 40</td>
</tr>
</tbody>
</table>

Abbreviations: Ad PEDF, adenoviral pigment epithelium-derived factor; ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD; AREDS II, Age-Related Eye Disease Study II; CAPT, Complication of AMD Prevention Trial; CNVM, choroidal neovascular membrane; CNVPT, Choroidal Neovascularization Prevention Trial; FOCUS, RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety; MARINA, Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular AMD; PDT, photodynamic therapy; PIER, Phase IIIb, Multi-center, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab; RCT, randomized controlled trial; SAILOR, Safety Assessment of Intravitreal Lucentis for AMD; siRNA, small interfering RNA; TTT4CNV, transpupillary thermotherapy for choroidal neovascularization.

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vascular AMD. Forty-five percent of the patients in the noninferiority to verteporfin PDT in the treatment of neovascular AMD was found that the drug did not meet the primary end point of the study. Thus, extended follow-up studies are needed.

The most promising anti-VEGF drug currently under investigation is ranibizumab. The 2-year Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR),

Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA),

and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) are currently under way. Other trials are investigating the effect of monthly intravitreal injection of ranibizumab (0.3-mg doses) vs verteporfin PDT, alone, or in combination with verteporfin PDT, respectively, for neovascular AMD. The 1-year results for each of these trials have demonstrated that ranibizumab maintained or improved visual acuity significantly better than the corresponding control treatment. The Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) trials and the Phase IIIb, Multicentric, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab (PIER) trials are investigating the effects of less frequent injection protocols in patients with neovascular AMD.

Although ranibizumab is not FDA-approved or commercially available, it is a fragment of the humanized antibody bevacizumab, which is FDA-approved for use in the treatment of colorectal cancer. Initial reports of off-label intravitreal bevacizumab in patients with neovascular AMD have been encouraging, but further studies are needed to better understand the precise risks and benefits associated with intravitreal injection of this drug.

The mechanisms by which steroids inhibit neovascularization are manifold. They include alterations in extracellular matrix turnover, inhibition of plasminogen activator, inhibition of inflammation and macrophage activation, and decreased vascular permeability. A number of steroid compounds are currently being studied in patients with wet AMD. These include intravitreal or periocular injection of triamcinolone acetonide and implantation of sustained-release steroid implants. Intravitreal administration of triamcinolone acetonide is associated with a risk of moderate to severe increase in intraocular pressure in 15% of patients and an increased risk of significant cataract progression requiring surgery in 20% of patients. The risk of endophthalmitis with intravitreal triamcinolone acetonide injection is estimated to be 0.1%. The long-term ocular sequelae of intravitreal steroids are not precisely known, thus extended follow-up studies are needed.

The C-01-99 phase 3 clinical trial of anecortave acetate found that the drug did not meet the primary end point of noninferiority to verteporfin PDT in the treatment of neovascular AMD. Forty-five percent of the patients in the anecortave acetate group lost fewer than 3 lines of vision compared with 49% of patients in the PDT group. Other trials of anecortave acetate using a new injection protocol that minimizes reflux of the drug and using varying injection intervals and doses are under way.

Squalamine is a cationic steroid isolated from the dogfish shark Squalus acanthius that has both antimicrobial and antiangiogenic properties. A phase 3, double-masked RCT of intravenous injection weekly for 1 month and monthly for 1 year of squalamine lactate in patients with neovascular AMD is currently under way.

Combination Treatments. Due to the limited success of monotherapy for wet AMD, many investigators are turning to combination treatment targeting various points in the molecular cascade responsible for neovascularization to improve outcomes. For example, PDT with verteporfin is being studied in combination with the following agents: posterior subtenons or intravitreal triamcinolone acetonide, intravitreal squalamine lactate, intravitreal pegaptanib sodium, and intravitreal ranibizumab, and vatalanib (ADVANCE: Study of Vatalanib and Photodynamic Therapy With Verteporfin in Patients With Subfoveal Choroidal Neovascularization [CNV] Secondary to Age-Related Macular Degeneration [www.clinicaltrials.gov]).

**RECOMMENDATIONS FOR DR G**

Dr G has reached a crossroads with regard to his vision. Despite a proven course of treatment with PDT and intravitreal verteporfin, as well as experimental adjuvant intravitreal steroids, Dr G has lost central vision in his right eye and has developed a disciform scar. Since the neovascularization process has reached its final cicatricial stages, no further treatment is possible in the right eye. Although his vision is still good in his left eye, the visual disability caused by his AMD has had a dramatic impact on Dr G’s ability to work and his quality of life, and consequently has resulted in a reactive depression.

Given the fact that he has both large soft drusen and pigmentary RPE abnormalities in his good eye and that his fellow eye has a disciform scar, Dr G has a 50% risk of progression to severe AMD in his good eye over the next 5 years.

I would recommend first that Dr G obtain the best possible refraction for his good eye to maximize his distance and near vision. He may also want to be seen by a visual rehabilitation specialist who may provide him with adaptive strategies for overcoming his functional limitations.

Second, Dr G should aim at minimizing the 10% risk per year that his good eye will progress to advanced AMD. In...
addition to encouraging a diet of fruits and vegetable (high in antioxidants and zinc), fish (high in omega-3 fatty acids), and nuts, and addressing any cardiovascular risk factors, such as smoking, hypertension, and elevated cholesterol, I would also recommend that he begin taking the AREDS-recommended antioxidant and zinc formulation on a daily basis. Based on the results of the AREDS study, we would expect that his risk of developing advanced AMD would drop from 10% to 7.5% per year, a 25% risk reduction, by taking these supplements. Dr G and his primary care physician should consider the proven benefits of these high-dose antioxidants and zinc with the small risk associated with beta carotene in someone with a remote history of smoking and high-dose vitamin E. He should be aware that there is some evidence that calcium channel blockers may increase the risk of progression to advanced AMD.

Third, Dr G should seriously consider joining one of the AMD prevention trials listed above. Such a trial intervention may possibly decrease his risk of AMD progression and would help push forward our understanding of this insidious disease.

Fourth, Dr G should be aware of the early symptoms of early subretinal CNV such as acute, unilateral loss or distortion of vision. He should test his vision daily using an Amsler grid and should seek immediate ophthalmologic care if he develops any of these visual changes in his good eye.

Finally, if Dr G has not already been evaluated for symptoms of his depression, he should be assessed to determine what treatment is indicated.

**QUESTIONS AND ANSWERS**

**QUESTION:** If you have an illness that is of consequence and affects 15% of the people over 85 years of age and you’ve got some evidence that you can slow its progression with this cocktail that you talked about, isn’t there an argument that you should give this prophylactically to people with good vision?

**DR ARROYO:** The AREDS study found that daily high-dose antioxidants and zinc supplements were associated with a 25% reduction in the risk of progression from moderate AMD to advanced AMD. They did not, however, find a benefit in patients with less severe AMD. Since high-dose beta carotene and vitamin E have been associated with an increased risk of lung cancer in smokers and mortality in patients with heart disease or diabetes, respectively, indiscriminate use is not advised. I recommend that patients who are older than 50 years of age be examined for evidence of macular degeneration, and that patients with at least moderate AMD should consider taking daily high-dose antioxidant and zinc supplements as per the AREDS study. Any patient who has a family history of AMD or has any sign of AMD should be aware of the risk factors associated with AMD and should be encouraged to modify risks accordingly.

**QUESTION:** Can you show us the data regarding control of high blood pressure and cholesterol levels?

**DR ARROYO:** As mentioned previously, hypertension and level of hypertension is associated with increasing risk of AMD. The association between cholesterol/lipid levels and AMD has been mixed. The relationship between statin use and AMD has also been quite variable, with the largest studies suggesting no association, and smaller studies reporting contradictory findings. Unfortunately, there are no prospective randomized studies that have studied the benefit of controlling high blood pressure or cholesterol on the incidence or progression of AMD.

**QUESTION:** Do you see a role for stem cell transplantation?

**DR ARROYO:** As you know, the retina is the most accessible part of the brain and is partially immunoprivileged. Because of these features, the retina will be a particularly good place to deliver stem cells in patients with retinal degeneration associated with AMD, retinitis pigmentosa, and retinal detachment. The treatment of ophthalmic disorders with stem cells is one of the most exciting and promising areas for future research.

**REFERENCES**


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Language is the archives of history. —Ralph Waldo Emerson (1803-1882)