AGE-RELATED MACULAR DEGENERATION:

RECENT ADVANCES AND HOPE FOR THE FUTURE

By Stephen Meffert MD, FASRS

HUMANS ARE VISUAL CREATURES. The familiar phrases "seeing is believing" or "a picture is worth a thousand words," "keep an eye out," and "turn a blind eye" are not accidental, but reflect the sensory bias of our physiology. A human's sense of smell or hearing is unremarkable in the animal kingdom, but our vision ranks with the best. Fully 50% of our brain's neurons are involved in analyzing visual input.

As we age physically, and often become more sedentary, our vision becomes even more vital to our quality of life. Thus, it is particularly poignant that, for those past retirement age, the risk of central vision loss from age-related macular degeneration (AMD) increases with each passing decade. In the United States, AMD is the most common cause of vision loss in people over the age of 65. By age 85, nearly 50% of Americans have at least some form of the disease.

Major research commitments have been made over the past several decades to understand the basic science of AMD and to identify potential therapeutic targets. We are beginning to see this work bear fruit with improving treatment options, and there is great hope for even more effective therapy in the foreseeable future. As a physician, it's exciting to be involved in a rapidly advancing field of medicine that offers such tangible patient benefits.

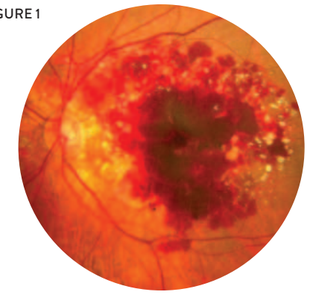
AMD OVERVIEW

Macular degeneration is primarily a genetic disease that affects individuals over the age of 60. Almost three-quarters of individuals with AMD have underlying associated genetic factors. AMD runs in families and tends to be more common in those of European descent. Lifestyle factors also play a role: smoking increases risk while a Mediterranean diet, exercise and weight control reduce risk. Vitamin supplements, as per the age-related eye disease study (aka AREDS2 vitamins, see sidebar on page 17), are thought to reduce the risk of severe vision loss in people with intermediate or worse macular degeneration.

Macular degeneration occurs, not surprisingly, in the macula, an anatomical region of the retina responsible for our central (or reading) vision. The macula is the only part of the retina capable of color vision.

There are two types of AMD: non-exudative (dry) and exudative (wet). Nearly all patients who develop AMD initially

FIGURE 1



develop "dry" or non-exudative macular degeneration. The dry form is essentially a loss of retinal cells and function. Cells die in the outer retina where the photoreceptors (rods and cones) reside. Geographic atrophy is an advanced form of dry macular degeneration with total and confluent loss of outer retinal cells. With the loss of the photoreceptors, vision is reduced. Most patients (85%) have only the dry form of AMD. Vision loss can be severe, but progression tends to be slow.

Of the patients with AMD, 15% develop the "wet" or exudative form, which involves the growth of abnormal new blood vessels (neovascularization). These new blood vessels can bleed and leak fluid, hence the "wet" terminology. Exudative AMD is responsible for 85% of the severe vision loss in AMD overall, and progression can be very rapid, even over a few days. Untreated, this form of AMD leaves a scar or fibrosis within the macula, often resulting in irreversible severe vision loss.

EVALUATION FOR AMD

The American Academy of Ophthalmology recommends that all individuals have a complete eye examination at 40 years of age. Based on findings and history, the ophthalmologist will recommend a follow-up plan. Past the age of 65, examinations should be performed every 1-2 years. Your primary optometrist (OD) or ophthalmologist (MD) will likely be the first to detect signs of macular degeneration and may recommend referral to a retinal specialist for further evaluation and possible treatment.

Retinal specialists are ophthalmologists with additional years of fellowship training in diseases and surgery of the posterior segment of the eye (retina and vitreous). When visiting your retinal specialist, you will undergo additional testing, often including optical coherence tomography (OCT) scans to evaluate the retinal layers, wide-angle color photography and, possibly, retinal angiography (see sidebar on page 17). After testing, the retinal specialist will examine your eyes and review your studies to determine a recommended course of action. If no treatment is needed or indicated, recommendations will be made regarding diet, lifestyle, supplements and home monitoring to reduce the incidence of vision loss and enhance early detection going forward.

THE AMERICAN ACADEMY OF OPHTHALMOLOGY RECOMMENDS THAT ALL INDIVIDUALS HAVE A COMPLETE EYE EXAMINATION AT 40 YEARS OF AGE.

CURRENT TREATMENT

The severity and rapidity of vision loss in the wet form of AMD has made it an important target for therapy. Fortunately, research has improved our understanding of chemical signals related to the development of abnormal blood vessels that cause vision loss in wet macular degeneration. This understanding has led to the development of a class of drugs called biologics that use the body's own protein design (antibody-like proteins) to interrupt specific pathways that cause abnormal blood vessel growth.

The first biologic drug used in wet AMD was approved by the Food and Drug Administration (FDA) in 2004 to suppress blood vessel growth to a cancer tumor. Some enterprising retinal specialists quickly realized that this drug might also suppress the unwanted bleeding and swelling caused by wet AMD. This class of medication, vascular endothelial growth factor (VEGF) inhibitors, has completely revolutionized our ability to reduce vision loss in wet AMD. I often tell patients that anti-VEGF medications are equivalent to the invention of antibiotics to treat infections: a total game changer. VEGF inhibitors are not a cure, but with consistent monthly or bi-monthly intraocular injections, they enable us to preserve vision for many years in eyes that, untreated, would soon be legally blind.

It is important to minimize treatment both for patient safety and to reduce patient treatment burden. Anti-VEGF drugs continue to be refined to enhance their potency, making it possible for patients to extend the length of time between treatments. We are currently seeing improved medications to treat wet AMD introduced every one to two years.

FIGURE 2

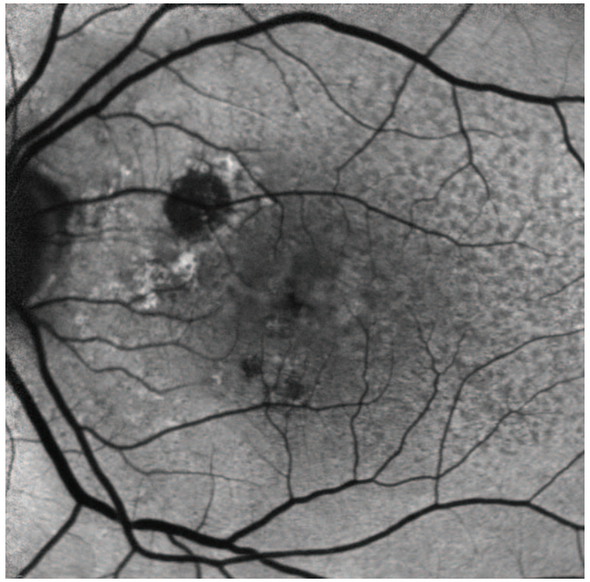


Figure 1. Wet macular degeneration with macular hemorrhage and thickening or edema

Figure 2. Autofluoresence image of non-exudative or "dry" macular degeneration where the darker and mottled areas represent cell loss or death.

FIGURE 3

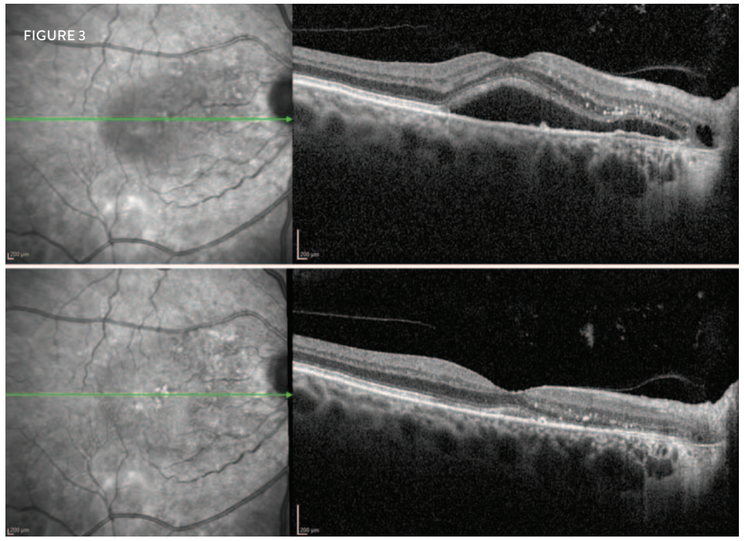


Figure 3. High-resolution optical coherence tomography produces cross-sectional images of the macula used for the diagnosis and management of macular disease. In the upper image, a patient presents with swelling (edema) of the macula from wet macular degeneration. The lower image is of the same patient one month after initial treatment. Note the marked decrease in swelling, which indicates that the wet macular degeneration is responding to treatment.

Therapy for the dry form of macular degeneration has advanced more slowly, and many candidate medications have failed to gain FDA approval. In 2023, the FDA approved the first drug for dry AMD, followed by a second drug six months later. (FDA approval implies that a group of experts have examined research and concluded that a drug is safe and efficacious.) Both drugs work to block the complement system (part of our immune system), a biochemical pathway selected as a therapeutic target because certain associated genetic variants are common in individuals with AMD.

Dry macular degeneration usually progresses very slowly, so treatment is less immediately gratifying, for both physician and patient, than for the wet form of the disease. After two years of treatment with monthly or bimonthly injections, a reduction in the rate of retinal cell loss may be detected, but no visual benefit has been shown. At best, the treatment for dry macular degeneration may produce some slowing of disease progression over long periods of relatively frequent treatment. In the future, we hope that longer periods of therapy may show measurable functional visual benefits.

FUTURE DIRECTIONS

Now that treatment is possible for many people with vision-threatening AMD, the next goal is to make treatment easier, safer and less expensive. Macular degeneration is one of the most active and innovative areas of research in medicine today. Many new treatment ideas are currently being studied. One of the more promising avenues of research is the insertion of genes in retinal cells that would allow the eye to produce its own medication and greatly reduce or eliminate the need for repeated intraocular injections.

Another innovative and exciting idea is that of photobiomodulation, in which the eye is exposed to controlled wavelengths and intensities of light. This may have beneficial effects in eyes with AMD through a complex (and incompletely understood) mechanism that likely involves multiple biochemical pathways at the cellular and cell organelle level. On November 5, 2024, the FDA approved the first photobiomodulation device for the treatment of AMD.

It's an exciting time to be a physician treating patients with macular degeneration. After years of being able to do so little for individuals suffering from this disease, it's extremely gratifying to have new and improving treatments for this devastating condition. For patients with AMD, it's a time of hope rather than a time of progressive, untreatable vision loss. ■

What Is AREDS?

The Age-Related Eye Disease Study (AREDS) and AREDS2 are major clinical trials sponsored by the National Eye Institute. The AREDS studies were designed to learn more about the natural history and risk factors of age-related macular degeneration (AMD) and cataract and to evaluate the effect of vitamins on the progression of these eye diseases. This work has produced the AREDS2 vitamins that are currently recommended for patients with intermediate or more advanced AMD.

The AREDS2 vitamin combination contains specific quantities of vitamin C, vitamin E, zeaxanthin, lutein, copper and zinc. It's the only vitamin or supplement with sufficiently large studies to support use in AMD and is widely available in local pharmacies.

Source: National Eye Institute

Diagnostic Tools

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) are non-invasive imaging tests. They use light waves to take cross-section pictures of your retina. With OCT, your retinal specialist can see each of the retina's distinctive layers. This allows your physician to map and measure their thickness. These measurements help with diagnosis. They also guide treatment for AMD.

Wide-angle color photography offers a wide-angle view of the retina not available through standard photography. It's generally used to enhance patient understanding of their retinal disease or problem and to better explain the rationale for any recommended treatment. It is also possible to perform angiography with this system if there is a peripheral retinal vascular issue.

Retinal angiography may be performed by your retinal specialist to better visualize the blood flow within your retina and choroid through the use of fluorescent dye (fluorescein) and digital imaging/videography. This aids in the diagnosis of your retinal condition and allows your doctor to follow changes in your eye over time or to target treatment areas.

Source: American Academy of Ophthalmology