

Age-Related Macular Degeneration: Solving the Puzzle of a Complicated Disease



A Series by:

Real World Health Care
2020

Macular Degeneration is an incurable eye disease that is the leading cause of vision loss, affecting more than 10 million Americans.

Age-Related Macular Degeneration: Solving the Puzzle of a Complicated Disease is a recently published series of articles that spotlights the organizations and efforts dedicated to helping those with AMD live full lives through AMD-related research, treatment and patient services. Please accept this complimentary copy as our way of thanking you for your commitment to helping this community and advocating for healthier futures.

founding sponsor



HEALTHWELL
FOUNDATION®

When health insurance is not enough.®

www.HealthWellFoundation.org/RealWorldHealthCare/

CONTENTS

Spotlight on Macular Degeneration 3

Emily Burke, Ph.D., Director of Instruction, BiotechPrimer.com

American Macular Degeneration Foundation Piecing Together the Puzzle of Age-Related Macular Degeneration 6

American Macular Degeneration Foundation

People with Macular Degeneration Live Full Lives with Help from Ophthalmologists10

American Academy of Ophthalmology

Spotlight on Macular Degeneration

Editor's Note: The following article is reprinted with permission from the Biotech Primer WEEKLY newsletter. To subscribe to the WEEKLY, visit www.weekly.biotechprimer.com.

Spotlight on Macular Degeneration

Getting old is for the birds. Time has its way with nearly every part of us: skin, hair, muscles. Few changes are more alarming, however, than those to our eyes. There's more to old eyes than bifocals and cataracts though. One of the most common eye diseases is age-related macular degeneration (AMD). It affects more than 13 million people over age 50 in the United States. It's the leading cause of vision loss in this age group.

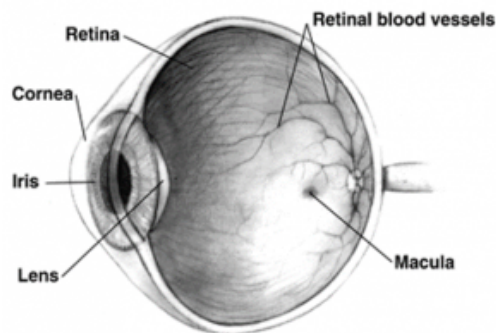
Eyes are spectacularly complicated organs: they contain over two million moving parts. You know some of the basics: iris, pupil, lens, retina. In some ways, this last, the retina, is more accurately considered part of the brain.

Term of the Week: Retina

The retina is composed of light-sensitive nervous tissue which forms a thin membrane that lines the rear two-thirds of the eyeball. It takes in light from the world around and converts into neural signals that travel along the optic nerve to the brain, telling us — “Hey, there’s an apple, or a laptop, or whatever.”



Emily Burke, BiotechPrimer.com



The anatomy of the eye (The National Eye Institute)

The macula is the small central area of the retina that enables central, high-resolution, color vision.

Macular Degeneration: A Gradual Loss of Vision

Macular degeneration progressively devastates eyesight, causing blurred vision and blocking the center of a person's visual field. What begins as a minor annoyance ends up making everyday tasks such as reading and driving impossible.

Ophthalmologists and other scientists don't know exactly what causes AMD. It is however, associated with a buildup of proteins and lipids just beneath the retina. These deposits, *drusen*, are a normal part of aging. However, the presence of larger or more drusen raises the risk of AMD. As the disease progresses, vision decreases. There are two types of AMD: neovascular (wet) or atrophic (dry).

Wet Age-Related Macular Degeneration (AMD)

In wet AMD, the infiltration of excess blood vessels is the main culprit. These abnormal vessels often leak fluid and blood, injuring the retina. Wet AMD progresses quickly, leading to loss of central vision without treatment. This form of the disease accounts for about 10 percent of cases.

FDA-approved treatments for wet AMD include Ranibizumab, Brolucizumab, and Aflibercept. These work by mopping up excess vascular endothelial growth factor (VEGF), which is what causes the excess blood vessel growth. Ranibizumab and Brolucizumab are monoclonal antibodies specific for VEGF. Aflibercept consists of the VEGF-receptor fused to the constant region of an antibody for stability. Similar to a mAb, this combination is called a fusion protein. It's highly specific for VEGF, binding it before it reaches its intended receptor on the surface of blood vessels. These VEGF-blocking treatments effectively stop the progression of AMD, but don't cure it.

KS-301 is an antibody-biopolymer conjugate (ABC), which also targets VEGF. An ABC is an antibody with a biopolymer—a chain of repeating subunits produced by a living organism—attached. In KS-301, the repeating subunits are lipids. They make the antibody more stable. That means patients can go up to five months between injections, compared to one month (**Ranibizumab**), two months (**Aflibercept**), or two to three months (**Brolucizumab**). The treatment is now in Phase II/III development.

These therapies are injected in the patient's eye, which makes them understandably unappealing. As an alternative, PAN-90806 is a small molecule inhibitor of VEGF that patients can administer at home by eyedrop. The drug has completed Phase I clinical studies.

It may be possible to do away with repeated treatments altogether with gene therapy. RGX-314 delivers a gene encoding an anti-VEGF antibody. In Phase I/II studies, participants produced the therapeutic protein, which controlled VEGF levels.

Dry Age-Related Macular Degeneration (AMD)

Dry AMD involves a gradual breakdown in the macula's light-sensitive cells. The dry variety progresses much more slowly than wet and accounts for about 90 percent of AMD cases. Advanced dry AMD occurs when cells in regions of the retina have wasted away and died. Sometimes these regions of atrophy (death) look like a map to the physician who is examining the retina, giving rise to the term "geographic atrophy" for late-stage dry AMD.

Currently, no treatments exist for dry AMD. However, some studies suggest that high doses of antioxidants including C and E vitamins, copper, zinc, and beta-carotene may slow its progression.

Inflammation, specifically the activation of complement proteins, is associated with drusen buildup and dry AMD progression. When they're activated, these immune system proteins interact, destroying targeted cells. Inappropriate activation of complement proteins can result in the destruction of healthy cells and tissue. A number of drugs in clinical development work by inactivating complement proteins:

- APL-2 is a peptide drug in Phase III development. APL2 binds to complement protein C3 and prevents its interaction with other complement proteins. Preventing this interaction prevents activating their destructive power.
- Avacincaptad pegol is a DNA aptamer in Phase II development. DNA aptamers are short strands of DNA that bind to a specific protein. Avacincaptad pegol binds to and inhibits complement protein C5.
- IONIS-FB-L_{Rx} is an antisense drug that blocks the production of complement factor B, currently in Phase II clinical testing.

Last month, the National Eye Institute announced preparations to begin clinical testing of stem cells for dry AMD. In the lab, researchers have coaxed stem cells to grow into retinal cells. In rodent and pig models, these cells restored vision, setting the stage for test human testing.

About Biotech Primer Inc.

Biotech Primer Inc. delivers current, relevant training to help professionals understand the science, business and regulatory processes essential to the biotechnology, pharmaceutical, molecular diagnostics and medical device industries. For more information, visit www.biotechprimer.com.

American Macular Degeneration Foundation Piecing Together the Puzzle of Age-Related Macular Degeneration

Macular degeneration is the leading cause of vision loss and blindness in those over 55. According to the [American Macular Degeneration Foundation](#) (AMDF), it affects more than 10 million Americans. After the age of 75, one in three Americans is at risk of developing this incurable disease.

While the cause of age-related macular degeneration (AMD) remains unknown, multiple, interconnected factors contribute to its development, including heredity, biological processes, age and environmental/lifestyle factors. Scientists are beginning to solve the puzzle of this complex disease, thanks in part to research funded by the AMDF.

“AMDF is committed to preventing, treating and curing macular degeneration through our national research agenda,” said Jennifer Williams, director of marketing for the AMDF. “At the same time, we offer hope and support to those with AMD and their families by raising public awareness of the disease, lobbying for increased federal research funding, and providing individualized educational resources.”

Age-Related Macular Degeneration Fueled by Nature and Nurture

AMDF takes a “broad impact” approach to the research it funds, supporting studies that significantly advance the likelihood of new treatments, unveil useable information about modifiable lifestyle factors associated with the disease, or create new opportunities to improve quality of life for all people affected by AMD.

“Minimizing the risk of developing AMD or slowing its progression requires a whole-body approach, rather than simply protecting your eyes with sunglasses,” explains Matthew Levine, AMDF Grants, Advocacy and Partnerships. “It involves creating a healthy balance between nature and nurture. While people may be born with certain genes that are associated with AMD, the extent to which those genes come into play is impacted by our environment and controllable behavior, including what we eat, how much we exercise, and whether or not we smoke.”

Biological Processes “Gone Wrong”

According to Levine, the current standard of care for treating wet AMD (the late-stage form of the disease that produces sudden, irreversible vision loss) is a routine, often monthly, injection of anti-VEGF (vascular endothelial growth factor) therapy into the eye, which suppresses the development of leaky, “rogue” blood vessels that can cause permanent damage to the eye’s rods and cones. Some patients find it difficult to adhere to the monthly injection schedule, and a significant percentage of patients don’t seem to respond to the therapy.

“Anti-VEGF therapy is currently considered the ‘last line of defense,’ and as a patient, it can be devastating to find out that you’re not responding to treatment as hoped,” said Levine. “However, recent research suggests that the ‘non-responders’ to anti-VEGF therapy aren’t really non-responders at all. Instead, these patients are responding earlier, and the drug is active for a shorter duration. A different, individualized treatment plan for this group of AMD patients may save the sight millions of people. This is an example of the type of broad impact research that AMDF seeks to support, and that may ultimately lead to a new understanding of how individualized this disease may be.”

Treating AMD with Gene Therapy

Researchers are continuing to identify and study the role of genes that are associated with degenerative diseases of the retina. The AMDF has funded a number of research projects in this area, notably the work of Johanna Seddon, MD, ScM, Department of Ophthalmology & Visual Sciences, University of Massachusetts Medical School, whose ground-breaking findings of AMD-related genes and their interactions with environmental factors (nutrition, smoking, body mass, etc.) have formed the basis for today’s early AMD management. Dr. Seddon is also co-author of AMDF’s “Eat Right for Your Sight,” a science-based cookbook for healthy eating to preserve vision.

Another AMDF-supported researcher, Neena Haider, PhD, Associate Professor of Ophthalmology at Harvard Medical School and Associate Scientist with the Schepens Eye Research Institute, has also broken new ground. Her work has resulted in the first FDA approval of a gene “modifier” therapy that doesn’t rely on knowing and replacing the exact genetic mutation involved in a disease, but rather the gene that controls the entire cascade of biological events that leads to the diseased state.

“Macular degeneration is different from many other diseases because multiple genes seem to play a role in the disease’s development,” said Dr. Haider. “In fact, we’re still trying to understand which genes, out of about 2,000, cause AMD and how those genes can be modified to prevent AMD. By modulating a gene that controls the pathways for inflammation, oxidative stress and protection from cell death, we can restore cells to their healthy state and prevent disease.”

Early AMD Detection

Levine noted that gene modifier therapies and other, new treatment approaches may prove to be particularly valuable when AMD is caught early, before the development of waste deposits beneath the retina, known as drusen, which are currently considered the earliest indicators of AMD. Recent research has established that the earliest indicator of AMD is the inability to quickly adapt to dark environments, as when entering a darkened theater on a bright day. Most people’s eyes adapt fairly quickly, but in those with AMD, the adaptation period is quite prolonged, making it difficult, for instance, to drive at night against oncoming headlights followed by a stretch of unlit road.



Johanna Seddon, University of Massachusetts Medical School



Neenah Haider, Harvard Medical School & Schepens Eye Research Institute

“Testing for compromised dark adaptation can detect AMD up to three years before the appearance of drusen, before patients experience any changes in their field of vision and central sight, and can allow patients to start making healthy lifestyle choices,” said Levine. “As with any progressive disorder, early detection and intervention can slow progression and, in the case of AMD, preserve sight.”

Precision Medicine Approach to AMD

The AMDF also is supporting Dr. Haider’s work in two other areas. One focuses on developing retina organoids —retina cell groupings grown from an individual patient’s blood or skin cells that are then turned into stem cells. These “retinas in a dish” will be used to test personalized medicine therapies with both FDA-approved and novel agents. The other area of research focuses on uncovering relevant “signatures” of patients’ microbiomes — the collection of microorganisms that inhabit our bodies and play a significant role in disease.

“The microbiome is unique to both individuals and sub-populations and is something you can change with diet and lifestyle choices,” Dr. Haider explained. “It’s another good example of how we can approach, attenuate and treat a disease by focusing on both our genetics, or nature, and our environment, or nurture.”

Immunotherapy for AMD

The AMDF also is supporting research into the role of the immune system in regulating AMD, through grantee [Kip Connor, PhD](#), Associate Professor of Ophthalmology at Harvard Medical School and Associate Scientist at Massachusetts Eye and Ear. According to Dr. Connor, the body’s immune system is vital not only in staving off infection, but also in helping clear our own body’s cells that have been damaged due to stress or injury.

“This is especially important in the brain, of which our retina is a part,” he explained. “If a retinal neuronal cell dies, we cannot make more, so when these cells become injured our immune system has to carefully remove them so they don’t injure their neighboring cells. Once we lose a neuron, we cannot replace it like other cells in our body, so keeping these cells around as long as possible is vital to maintaining our vision.”

Dr. Connor added that as we age, these immune regulatory systems can become dysfunctional or overactive, which drives the disease pathology and the resultant loss of vision. He pointed to a number of immune pathways that are being investigated in the pathology of AMD, including one of the oldest evolutionally conserved immune pathways, the Complement system. The Complement system has been implicated as a risk factor for AMD, with a 50 percent increased risk of developing the disease in individuals with a mutated form of one of the proteins in the pathway. More recently, the role of resident immune system scavenger cells of the retina, microglia, has become an area of intense investigation, including how these cells become activated — and when — throughout the disease course.



Kip Connor, Harvard Medical School

Stem Cell Treatments for AMD and Beyond

According to Levine, AMDF-supported scientists and others are developing stem cell replacement therapies for the retinal pigment epithelium (RPE), the tissue behind the retina that provides the retina with nutrition

and removes debris generated by the eyes' photoreceptor cells. Patient-derived, lab-grown RPE cells are placed into a biologically based "scaffolding" that is surgically implanted behind the retina to create and maintain a better environment for the photoreceptor cells. Recently, the National Eye Institute (NEI) announced the first human clinical trial to test the safety of this approach to treat geographic atrophy, the advanced "dry" form of AMD.

For people with low vision from AMD, artificial retinas may offer hope as well. The artificial retina is a tiny camera and video processor mounted on a pair of glasses, which communicates wirelessly with a sheet of electrodes implanted in the eye. The camera collects light signals and transmits them through the electrodes to the brain, bypassing the damaged retina. The more electrodes, the better the technology works.

From the Lab to the Clinic

While the AMDF's funding of AMD research is leading to real gains in approved treatments, the Foundation's Williams noted that an AMD diagnosis is still overwhelming for most patients.

"We've conducted surveys about communications between patients and doctors and have found that information about treatments — and especially the important lifestyle modifications that can slow the disease's progress — isn't always delivered or received," she concluded. "Sometimes the advice to eat well, get exercise, wear eye protection and not smoke seems so simplistic that people ignore it, and the disease progresses. The AMDF is developing initiatives to improve treatment outcomes by overcoming those communications obstacles."

For more information, visit the [American Macular Degeneration Foundation](#) and follow Real World Health Care's coverage of [Age-Related Macular Degeneration](#).

People with Macular Degeneration Live Full Lives with Help from Ophthalmologists

Does a diagnosis of age-related macular degeneration (AMD) mean you can't live a rich, fulfilling life? Not necessarily, according to the experts.

"The initial diagnosis can be scary," said Purnima S. Patel, MD, associate professor of ophthalmology at Emory University who also works at the Atlanta VA Medical Center and serves as a clinical spokesperson for the American Academy of Ophthalmology. "People hear about the in-eye injections that are standard therapy and think, 'there's no way I can do this.' They should know that their ophthalmologist can help them adapt to their situation and make the most of their vision. Plus, those injections aren't nearly as gruesome as everyone fears."

Start Screening for Macular Degeneration Early

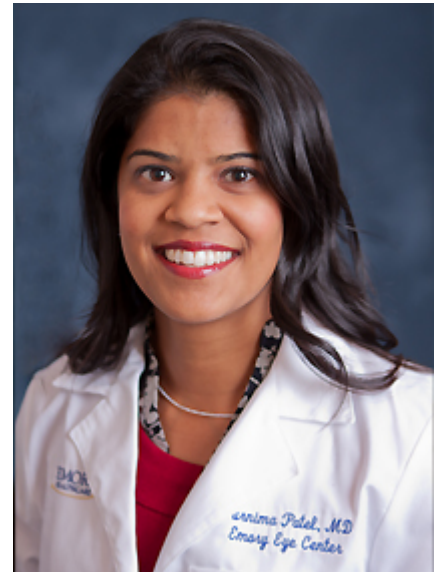
As its name suggests, AMD is a product of aging. The most common form of AMD, dry AMD, happens when parts of the eye's macula (part of the retina) get thinner with age. Tiny clumps of protein called drusen grow and central vision is slowly lost. The less common, but more serious, wet AMD happens when abnormal blood vessels grow under the retina and leak blood or other fluids that cause scarring on the macula. Vision loss is faster with wet AMD than with dry AMD.

The most common symptoms of AMD are vision distortions: straight lines that look wavy or bent, "splotchy" looking central vision, or being able to see some things but not others. Side, or peripheral, vision is not affected by AMD.

"Patients may have these symptoms and not even know it," Dr. Patel said. "That is why we encourage adults to visit an ophthalmologist for a baseline screening at around age 40, when eye conditions start to manifest. By age 65, people should be screened annually."

Dr. Patel added that annual screenings are particularly important for people with high risk factors, including a family history of AMD, light skin, smoking, being overweight, and having high blood pressure, high cholesterol or heart disease.

"The best prognosis for maintaining or recovering your vision is based on the strength of your vision at the time of diagnosis," she said. "An ophthalmologist can stay attuned to any nuanced changes."



Purnima S. Patel, MD, Emory University

Macular Degeneration Treatments: What to Expect

According to Dr. Patel, there is no cure for dry AMD. However, she typically recommends that patients with this common form of AMD take a vitamin formulation known as AREDS-2. Clinical studies of AREDS show that the formulation may delay progression of advanced AMD and help maintain vision longer in patients with intermediate AMD or AMD in one eye.

She also recommends an eye-healthy diet including lots of leafy greens, not smoking, and wearing UV eye protection, even on cloudy days—advice applicable to those with both dry and wet AMD.

“Ophthalmologists may send patients home with an Amsler grid,” she added. “It lets patients monitor each eye to help detect those subtle vision changes that aren’t always obvious because they come about so slowly.”

Treatments for wet AMD have evolved significantly over the past 10 years, according to Dr. Patel. Today, the standard therapy involves monthly injections of anti-VEGF drugs, which help reduce the number of abnormal blood vessels in the retina and slow blood vessel leakage.

“These injections aren’t a cure, but they can control and stabilize vision loss,” she said. “Your ophthalmologist will apply a sterilization solution to prevent infection as well as numbing drops before inserting a very slender needle into the eye. The whole process is a lot less painful than most people fear.”

Dr. Patel added that some patients report a gritty or sandy feeling in the eye following injections, but most people can go about their daily activities immediately after treatment as long as they avoid getting their eye dirty—so no swimming or lawn mowing, for example.

Living with Macular Degeneration

According to Dr. Patel, most people with macular degeneration live full lives, with minimal impact on activities of daily living.

“Because the central vision is affected, activities like reading and watching TV can be challenging,” she said. “However, since peripheral vision isn’t affected, people can still get around.”

She encourages those with MD to ask their ophthalmologist about assistive devices such as magnifiers and other tools and electronics designed specifically for those with low vision.

“I take care of people with macular degeneration every day and I’m in awe of the amount of resilience they have and the way they continue to thrive with the various treatment options and tools at our disposal,” concluded Dr. Patel.