

## Introduction

Here is MD Support's summary of the past twelve months of significant research and development in the field of macular degeneration.

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## PHARMACOLOGY

### Infection From Avastin

The big pharmaceutical news of the year surrounded anti-VEGF drugs for treatment of wet AMD. VEGF stands for a protein called "vascular endothelial growth factor". Anti-VEGF drugs are injected into the eyeball to block this protein and halt the growth and leakage of blood vessels into the retina that can lead to quick central vision loss. The leading approved drugs are Lucentis and Eylea, while a similar drug, Avastin, is being used off-label for the same purpose at a much lower cost. Repackaging by a pharmacy, however, is required to prepare Avastin for injection at proper dosages.

In September, the FDA alerted the public that repackaged intravitreal injections of off-label Avastin caused a cluster of strep infections in twelve patients in Florida, where investigators traced the tainted drug to a single pharmacy. Soon after, contamination was also reported in Tennessee and California. This is a risk that Genentech, the maker of the drug, warned about when doctors began using the cancer drug Avastin in place of their approved drug, Lucentis.

Reacting quickly to the reports of infection, the Department of Veterans Affairs (VA) ceased using Avastin to treat wet AMD until it could investigate the problem. Then, in November, the VA announced the reinstatement of Avastin on three conditions: 1) that the physician use only one dose per patient from each manufacturer's vial, 2) that patients be carefully screened before receiving treatment, and 3) that patients be fully informed of the health risks associated with off-label therapy.

Many patients contacted MD Support asking what they should do to ensure their safety. Our recommendation was to learn about the benefits and risks of all three available treatments, and then decide which is better in the patient's individual case. It is the doctor's obligation to ensure that the patient has a full understanding before agreeing to receiving Avastin off-label.

Ophthalmic use of Avastin has recently been shown to be generally as safe and effective as Lucentis. Since, however, both the Food and Drug Administration and the Center for Disease Control have established clear warnings and specific guidelines about repackaging drugs, and since those guidelines are generally being ignored in the use of off-label Avastin, a patient's safest option is to stick with proven drugs that don't require compounding by a second party. In his article, "The Misuse of Compounding By Pharmacists", Bruce A. Bouts, MD recommends that our best practice would be to:

1. Avoid compounded agents when sterility is important (e.g., injectable or inhalation agents).

2. Avoid a compounded product when a generic or brand-name agent is readily available.

## Eylea

In November, our attention was drawn to FDA approval of the newest anti-VEGF drug, Eylea, as a treatment for wet AMD. In trials, Eylea injected into the eye every two months was found to be as effective as monthly doses of Lucentis. The most striking improvement is that monthly monitoring of patients receiving Eylea is not necessary. The longer time between injections (up to two months) helps relieve some of the treatment and cost burden of other anti-VEGF drugs.

This would seem to give Regeneron (the company that makes Eylea) the edge over Genentech, makers of Lucentis. And it did indeed take over a large share of the market within only a few months. Genentech and its European counterpart, Novartis, however, are remaining big players by working toward first approval of Lucentis for use in treatment of diabetic macular edema.

## Long-lasting Lucentis

Another development from Genentech may soon be availability of sustained long-term delivery of Lucentis by way of an implanted ocular device. This would replace the current procedure of periodically injecting the drug into the eyeball.

The device can be implanted into the eye in a 15 minute out-patient procedure. The implant can hold and release four months worth of Lucentis, and it can be resupplied through a permanent opening where it attaches to the sclera (the white outer shell of the eyeball). About 100 implants have been accomplished to date, and the results are consistent with the traditional injection procedure. According to Genentech, The patient would not be aware of the device, and it can be seen only upon examination through the dilated pupil. Trials are expected to begin soon, with clinical use possible in as little as two years.

## MC-1101

In May of this year, a topically administered eye drop drug called MC-1101 was introduced as a potential for treating and stopping the progression of AMD from the dry form to the wet form. The drug, being tested by MacuCLEAR, Inc., works by increasing ocular blood flow in the choroidal vessels.

The company has completed a successful Phase 1 human clinical trial for MC-1101 which showed that the drug is safe and well tolerated. The next phase of the study will track visual improvement in 60 patients, with the hope that a treatment for dry AMD will soon make it to the clinics.

## Fenretinide

But now some disappointing news. Fenretinide, a drug that has been used to treat certain cancers, rheumatoid arthritis, acne, and psoriasis, was found several years ago to slow the production and accumulation of a toxin that leads to vision loss in a juvenile form of macular degeneration called Stargardt disease. Trials showed that the drug also reduced

the incidence of choroidal neovascularization by about 50 percent in patients with dry AMD.

This was promising news worth following, but the developer, Sirion Therapeutics, announced in February that the trials had been suspended. The FDA ruled that the Phase 2 results were flawed, and, at this point, the high cost of continuing the trials has halted further research.

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## SURGERY

### Implantable Miniature Telescope

In the field of surgery this past year, we heard about approval of the implantable miniature telescope, ongoing stem cell research, and an interesting development in treatment for cataracts.

You may remember that the implantable miniature telescope (IMT) was approved by the FDA back in July 2010 for use as a prosthetic device in the eye. Then, in September 2011, VisionCare Ophthalmic Technologies, Inc. announced that outpatient facilities could obtain Medicare and Medicaid reimbursement for the procedure. Two months later, the company announced that the first patient had received the device.

The pea-sized telescope implant is designed to improve visual acuity. Eligible patients must have central vision blindness and have either stopped responding to AMD medications or have a form of the disease for which no treatment is available. The magnification provided by the implant reduces the impact of the blind spot caused by end-stage AMD. Patients and physicians can find more information about the IMT at [www.centrasight.com](http://www.centrasight.com).

### Stem Cell Study

Another bit of good news came in January of this year from Advanced Cell Technology, when the company reported the first use of human embryonic stem cells to treat macular degeneration in human beings.

The study began with one elderly patient and one young patient with different forms of macular degeneration that had led to severe vision loss. The transplants appeared safe after four months, and both patients had some improvement in vision. The future therapeutic goal will be to treat patients earlier in the disease process, in order to boost the prospects of improving or retaining sight in new patients.

The authors say that, in patients who begin with poor vision, it is difficult to ascertain definite improvements in vision unless such improvements are spectacular. While neither patient lost vision, some standard tests suggested vision had improved in both. The younger patient with Stargardt's disease went from being able to see only hand movements at first to being able to see single finger movements.

The study is expected to continue into 2014, beginning with 12 patients and eventually including a much larger population. Clinical trial sites have been established so far at Jules Stein Eye Institute in Los Angeles, Wills Eye Institute in Philadelphia, Bascom Palmer Eye Institute in Miami, and Massachusetts Eye and Ear Infirmary in Boston.

### Radiation Therapy

Five years ago, NeoVista, Inc. began trials to study the effects of radiation therapy in combination with Lucentis injection for treatment of wet AMD. The therapy was intended to complement the drug injection by extending the time between treatments. Unfortunately, the company reported in February that Phase III of the study did not meet its primary endpoint at two years, becoming the second major trial to fall by the wayside this past year.

## HuCNS Cells

Returning to a more positive note, we heard good news in February about stem cell research from StemCells, Inc. They announced that the FDA authorized a trial of a new method using stem cells from the brain to prevent degeneration of the macula in dry AMD patients.

Purified human neural (HuCNS) stem cells will be administered by a single injection into the space beneath the retina. Patients' vision will be evaluated over a one-year period, then followed for an additional four years in a separate observational study.

Preclinical data submitted by the Company demonstrated that the stem cell transplants significantly protect against the degeneration of the existing sight cells. Moreover, the number of cone cells (which are responsible for central vision) remains constant over an extended period. This approach is expected to offer a safe, effective and simple treatment that differs from approaches that aim to replace the sight cells.

## Cataract Surgery and Alzheimer's

Our final report in the surgery department comes from a study showing that cataract surgery can relieve Alzheimer's symptoms in some people.

As reported by the researchers in April, one in four patients showed improvements in thinking and memory skills after replacement with a clear lens. Many also showed an easing of symptoms of depression, and most of the participants also slept better after the surgery. They did not show improvements in day-to-day functioning, but all-in-all, that's not bad, considering they could do all that and see better, too.

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## NUTRITION

### Vitamins and Aspirin

Moving on to developments in the field of eye health and nutrition, two studies published last year caused some concern in the low vision community about possible harm from vitamins and aspirin. We may be worrying more than necessary, however, due to the way the study results were reported.

One study concluded that "several commonly used dietary vitamin and mineral supplements may be associated with increased total mortality". The other study revealed that frequent aspirin use is associated with early AMD and wet late AMD.

Both of these studies have three things in common: 1) use of terms like "associated", 2) the absence of cause and effect in the study designs, and 3) media distortion of the facts.

We must remember that a certain intervention "may be associated" with macular

degeneration, but it does not necessarily cause the disease or its progression. For example, a person may be taking regular dosages of aspirin to alleviate a cardiovascular problem. At the same time, that person may have macular degeneration caused by the same inflammatory response responsible for the cardiovascular condition. There would, therefore, appear to be an association between aspirin and macular degeneration.

The researchers are aware of this, which is why they have not said conclusively that either vitamins or aspirin are going to harm us. They simply say that an association has been found and that further study is necessary before making such claims. It is the media that often carries it to that next step. We must, therefore, think twice about such reports and consult with professionals before changing our course of treatment.

## AREDS2

Since 2006, the National Institutes of Health (NIH) have been conducting a nationwide study to see if a modified combination of vitamins, minerals, and fish oil can further slow the progression of vision loss from AMD.

This new study, called the Age-Related Eye Disease Study 2 (AREDS2), builds upon results from the first AREDS research. That study, completed in 2001, found that high-doses of vitamins C and E, beta-carotene, zinc, and copper, taken by mouth, reduced the risk of progression to advanced AMD by 25 percent, and lowered the risk of moderate vision loss by 19 percent.

AREDS2 will refine the findings of the original study by adding the antioxidants lutein and zeaxanthin and the omega-3 fatty acids DHA and EPA to the formulation. The main objective is to determine if these nutrients will also help decrease a person's risk of progression to advanced AMD. Previous observational studies have suggested that these nutrients may protect vision.

In addition to including these nutrients, the study is also looking at eliminating beta-carotene from the original formula, due to findings that it may be a risk for cancer in some people, and it is decreasing the amount of zinc. Findings from the study are expected in 2013, but manufacturers are already making the AREDS2 formula available based upon a preponderance of evidence in its favor.

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## GENETICS

### Complement Factor H

In the area of gene replacement research, three events caught our attention during the past twelve months. We learned in November that investigators had identified a rare, high-risk mutation resulting in a loss of function of an important protein called Complement Factor H (CFH). CFH helps control the body's immune response and inflammation, and mutation of this protein has been suspected for several years to be a cause of AMD in as many as 50% of cases. Now a newly-discovered mutation, more clearly links the CFH gene dysfunction to the disease and may lead to new and effective preventative treatments for high risk individuals.

### AVA-101

In April, we heard about a single injection of a new gene therapy treatment from

Avalanche Biotech that could possibly stop blood vessel growth and leakage in the wet form of AMD for several years. An injection of a drug called AVA-101 creates a kind of BioFactory that continuously secretes a therapeutic protein over an extended period. This avoids the need for frequent injections, as is now the practice.

Based on preclinical studies, the therapeutic effect will be maintained for at least 18 months and has the potential to last for several years. Human clinical trials are currently underway.

## IL-18

In May, a new finding made the news as yet another possible treatment for wet AMD. Inflammation in the retina results from blood vessel development, and the natural component named IL-18 has been found to keep the process under control. By injecting the chemical into the eye, or by injecting a gene that produces IL-18, the scientists are speculating that they can keep dry AMD from developing into wet AMD. In other words, it would be a preventative treatment, similar to a vaccination.

This discovery was the first step in a long road to clinical application. It must first be tested in animals, then go through human clinical trials, so we are looking at about 10 years of intensive lab work and fund raising. If results from other treatment experiments underway don't come sooner, at least this offers another reason for hope.

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## TECHNOLOGY

### New Vision Enhancement System

And finally, technology continues to make strides. One development is a new vision enhancement system that may one day provide something like sight for people who are blind or extremely visually impaired. The system is being developed as a result of military-related trauma research.

It involves computer technology, a cell phone, an auditory feedback device, and an eyeglass-mounted camera to capture objects in the user's visual field. Information about the visual field is conveyed to the user wirelessly to assist in finding objects or avoiding hazards.

Developers say that, though the technology focuses on military vision trauma, it could also be used by people with age-related and other forms of macular degeneration.

### iPAD3

And, of course, 2012 has brought the latest generation of the Apple iPad to market. The iPad3 has a higher screen resolution than the iPad2, a better camera, and stronger wi-fi (at extra cost). Other than that, it is essentially the same as its older brother, and the changes may be too negligible for you to upgrade. On the other hand, if you don't already own an iPad, you can find really good deals on the older models for less than \$350. Considering all of its accessible features for low vision people, it might be worth looking into.

### Driving

Another exciting technological development is the self-driving automobile. It has been road tested now for thousands of miles, and it looks like it will actually become a reality in a few years. In case you think you couldn't afford one (and how many people could?), don't

worry. They are being seriously considered for use as taxis, so they will be available to all of us. And we won't have to talk to them about the weather, or why they drove a mile out of our way to get us to the grocery store on the next block. Just call a phone number, say "pick me up", and the automated car will come right to your front door.