



Treatments for Retinal Bleeding Caused by PXE

By Sophia Vourthis with Sharon Terry

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(The following information is about Age-related Macular Degeneration (AMD). Some individuals with PXE have choroidal neovascularization (CNV) and scarring, a similar problem that occurs in Age-related Macular Degeneration. Therefore, information about AMD is often useful to people with PXE.)

Development of “wet” age-related macular degeneration (AMD) occurs when abnormal blood vessels grow under the retina and macula, in a process known as choroidal neovascularization (CNV). CNV is the body’s misguided attempt to supply more nutrients and oxygen to the eye’s retina by creating new blood vessels. The newly formed blood vessels may bleed and leak fluid and cause the retina to bulge or lift up, thus distorting central vision. Further damage is done and central vision is destroyed when there is scarring of the retina. The abnormal growth of blood vessels in any part of the body is also known as angiogenesis.

Currently, there is no outright cure for AMD. However, some treatments may delay its progression or even improve vision. Success of any treatment—stopping further progress of the vision loss—depends on the location and extent of the abnormal blood vessels, or CNV. The more recently available treatments stem from work done in cancer research on the causes of angiogenesis—the growth of new blood vessels. Scientists discovered that there is a protein found in blood vessels feeding tumors and also in blood vessels in the eye, that encourages the

development of blood vessels called “vascular endothelial growth factors” (VEGF). Research has led to the development and use of antiangiogenic drugs that inhibit VEGF from stimulating growth. This article will discuss several of them.

Macugen®

In late December 2004, Macugen®, manufactured by Eyetech Pharmaceuticals & Pfizer, was the first antiangiogenic drug approved by the FDA to treat wet AMD. Macugen is injected directly into the eye by an ophthalmologist. It works by interfering with VEGF, thereby stopping the formation of new blood vessels and decreasing leakage from existing blood vessels.

Approval of this drug was based on two Phase 2/3 randomized, multi-center, doublemasked clinical trials involving approximately 1,200 patients with all subtypes of neovascular AMD (none of these had PXE). During clinical trials, patients injected every 6 weeks with Macugen showed less vision loss than those who received a placebo injection. More specifically, at the one-year mark, 70% of patients receiving Macugen lost less than three lines of vision on the eye chart compared to 55% in the placebo group. After the first year, patients were randomized to continue or discontinue treatment for an additional year. Two-year clinical data from the studies demonstrated that patients benefited from continued treatment with Macugen. Essentially, Macugen treatment was shown to slow down the progression of the disease but

did not seem to reverse damage already done. Unfortunately, only a small number of treated patients had significant visual improvement.

Macugen is generally well tolerated, but there are some drawbacks. The risks of receiving this treatment are largely attributable to the injection technique used, and not the drug itself. Over the 2-year study, 11,636 injections were administered. During this time a total of 6 traumatic cataracts and 10 retinal detachments occurred. The most common side effect during the clinical trial was infectious endophthalmitis (an inflammation of the internal structures of the eye due to injection) seen in 16 patients. It is important to note that 12 of the incidents occurred in the first year of the trial; most of these were due to violations of the protocol for sterile injection technique. In addition, not all patients are suitable candidates for Macugen. Macugen treatment is most beneficial for patients in the earlier stages of wet AMD. For those patients who have already lost significant vision, Macugen treatment may help slow down the rate of further vision loss but does not repair the damage that has already occurred.

Lucentis®

Lucentis® is another drug used to treat wet AMD by blocking the new growth of abnormal blood vessels, similar to Macugen. However, this treatment is injected into the eye more frequently—every four weeks instead of every six weeks. Before June 30, 2006, Lucentis was available only in clinical trials. Four different studies of Lucentis (again, none in PXE) were ongoing and had completed enrollment. Based on the clinical efficacy and safety data from two of these trials, as well as data from the additional two clinical trials, the new drug application for Lucentis was approved for treatment of AMD by the U.S. Food and Drug Administration (FDA)

on June 30, 2006. Genentech Pharmaceuticals is the manufacturer of the drug.

The two major trials are described below.

The first, named MARINA, is a Phase III study of 716 patients in the United States with minimally classic or occult wet AMD (see **Defining the Terms**), who were randomized to receive Lucentis injections or a control regimen. The control regimen consisted of a sham injection, meaning the treating physician prepares and anesthetizes the patient's eye but does not perform an injection. Patients in this study receiving the actual Lucentis injections were then further randomized to receive either a 0.3 mg or 0.5 mg dose once a month for two years. In July 2005, one-year results from MARINA were reported. Nearly 95 percent of patients treated with Lucentis had maintained or improved vision. In addition, 25 percent of patients treated with 0.3 mg of Lucentis and 34

Defining the Terms

Classic and Occult AMD: Occult AMD occurs when blood vessels grow and leak fluid under the retinal pigment epithelium (RPE). The RPE is the layer outside the retina that nourishes the retinal visual cells.

Classic AMD usually occurs when abnormal blood vessels grow above the RPE, further distorting vision.

Cataract: A cloudiness of the lens of the eye which prevents the passage of the rays of light and impairs or destroys the sight.

Off-label use: The term "off label" is used when a drug is used for something other than for which it was approved. Example: Avastin was approved to treat colorectal cancer, and it is being used to treat AMD.

percent treated with 0.5 mg Lucentis improved vision by a gain of 15 letters (3 lines) or more compared to approximately 5 percent of patients in each of the control groups. Patients treated with Lucentis, regardless of dosage, gained an average of 7 letters in visual acuity compared to study entry, while those in the control group lost an average of 10.5 letters.

Preliminary two-year data from MARINA showed that the improvement in the Lucentis groups at year 1 was maintained at year 2 as measured by visual acuity endpoints, while there was further deterioration of vision among patients in the control group.

A more recent study, ANCHOR, compared Lucentis injections to photodynamic therapy with Visudyne (PDT) for the treatment of predominately classic CNV among 423 patients. This study is ongoing in the United States, Europe and Australia. During the first year of this two-year study, approximately 94 percent of patients treated with 0.3 mg of Lucentis and 96 percent of those treated with 0.5 mg of Lucentis had maintained or improved vision compared to 64 percent of those treated with PDT. Also within this first year, patients treated with 0.3 mg of Lucentis gained an average of 8.5 letters, and those in the 0.5 mg group gained an average of 11 letters compared to patients treated with PDT, who lost an average of 9.5 letters.

Avastin®

Avastin® has been used in the treatment of colorectal cancer since 2004 and has the same mechanism of action in the retina as it does in cancerous tumors: it blocks the formation of new blood vessels. Currently, Avastin is being used offlabel and in clinical trials in the therapy of other cancers, including lung, breast, and renal carcinomas. Avastin was initially considered as an antiangiogenic therapy for CNV; however, because it is such a

large molecule it was deemed unlikely that it would penetrate the full thickness of the retina during injection.

In early 2004, a group of ophthalmologists in Miami, Florida initiated the use of Avastin in the treatment of AMD for patients that were not candidates for or were failing other therapies. The first study they conducted was called Systemic Avastin for Neovascular AMD (SANA). In this and subsequent studies, they clinically followed a small number of patients and reported improvements in visual acuity comparable to Lucentis with no serious adverse events. However, it is important to note that these clinical studies were not conducted as randomized clinical trials. Since then, offlabel use of Avastin has become increasingly popular, but guidelines for its use have yet to be established.

The concern among some doctors and for Genentech Pharmaceuticals (developers of the drug) is that there have been no randomized controlled clinical trials, nor are there any scientifically accepted published reports regarding proof of safety or demonstrated efficacy for the drug's use in retinal therapy. Another major concern includes the fact that Avastin does not contain any preservatives, so there could be problems in keeping it sterile when it gets split up into small quantities for injection. Also, Avastin clears from the system 100 times slower than Lucentis. Remaining in the retina for that length of time could be harmful.

In order to develop Avastin into a drug proven safe and effective for wet AMD, Genentech says that it would have to start at the pre-clinical stage of a clinical trial. The company maintains that a time involvement of 5-7 years would be fruitless when Lucentis (also manufactured by Genentech) is already approved and proving its value. In addition, treating a

patient with Lucentis is more expensive, and, therefore, Genentech has little incentive to go through the laborintensive, costly process of submitting Avastin for FDA approval.

You can obtain more information regarding

available treatments and therapies on the horizon from the following sources:

www.mdsupport.org
www.amdalliance.org
www.macular.org
www.gene.com
www.webmd.com

What does this have to do with PXE?

This article describes treatment for Age-related Macular Degeneration (AMD). People who are affected by PXE experience a process in their retina similar that experienced by those with AMD. However, people with PXE have angioid streaks (breaks in the membrane beneath the retina); people with AMD do not. The cause of the process of blood vessel growth, bleeding and vision loss is different for the two diseases. They are different diseases.

However, just as for other signs and symptoms of PXE, current treatments for other conditions sometimes offer a solution. PXEers have a long history of using treatments designed for AMD: traditional laser, photodynamic therapy (PDT), steroid treatments, and submacular surgery, among others. These treatments and therapies are always used off-label. While this is perhaps good for the individuals using the treatment, it doesn't give us information about these treatments and PXE in general. For that we will need PXE clinical trials.

Our Capital Campaign will be culminating this year. We are only \$25,000 short of the \$300,000 we need to conduct a 3-year clinical trial of these treatments and PXE. We have discussed this with scientists at NIH and will make an announcement about the trial as soon as we raise the rest of the funding! This trial will tell us a great deal about what treatment is effective, and perhaps prevent the next generation of PXEers from losing their vision. If claims made about vision being restored with some of these drugs are true, then perhaps there is also hope for those with vision loss today, as well. In any case, we continue to vigilantly explore these drugs and other therapies for all of you, our members. To receive information about the trial as soon as it is available, send your email address to Mary LeBlanc mleblanc@pxe.org, our wonderful email list manager.