Regeneron Focuses on Age-Related Macular Degeneration

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For some people, the onslaught of time brings another loss: the erosion of central vision, making it impossible to drive or read a book or see the contours of a loved one's face. No one knows what precipitates age-related macular degeneration (AMD), but it is the leading cause of vision loss among the elderly in western countries. Aside from getting old, the major risk factors for AMD include smoking and having a genetic predisposition.

Approximately 15–20 million Americans suffer from AMD, with about 200,000 new cases diagnosed each year and 3–4 million legally blind as a result. No cure exists; current therapies can slow disease progression in a limited number of cases, but do not address the underlying cause.

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The macula is a small patch in the middle of the retina that contains a high concentration of photoreceptor cells which transmit visual signals to the brain and governs central vision. Macular degeneration takes two forms: the early atrophic, or "dry," and the more advanced exudative, or "wet," version. Most people develop the early or intermediate dry form of macular degeneration in which tiny deposits of protein and other cellular debris called drusen accumulate on the macula.

Some patients with dry AMD are helped by doses of vitamins and antioxidants. The Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute (NEI) showed that antioxidant supplements retarded progression of dry AMD in about one-quarter of cases. NEI is currently recruiting 4000 volunteers for a new study to see the effect of antioxidants (lutein and zeaxanthin) and/or the long-chain omega-3 fatty acids DHA and EPA.

In 10%–15% of patients, AMD abruptly morphs into the more virulent wet type, in which abnormal blood vessels grow uncontrollably beneath the retina, damage the macula, and leak blood and fluid. This process, called choroidal neovascularization (CNV), irreversibly damages the photoreceptor cells.

The first FDA-approved treatment for wet AMD was Visudyne (verteporfin) Photodynamic Therapy (PDT) from QLT and Novartis. Visudyne, a light-activated drug, is injected intravenously to destroy targeted blood vessels. Aside from surgery, other approaches under development include implants to deliver medication.

Sibling Rivalry

In the mid and late 1990s, it became increasingly apparent that vascular endothelial growth factor (VEGF) was a driver for CNV. VEGF antagonists such as Macugen (Pegaptanib), an injectable ribonucleic aptamer, was developed by Pfizer/Eyetech. Macugen was the first VEGF antagonist to get approved, in 2004, but the current gold standard for treating wet AMD is Genentech's Lucentis (ranibizumab), a humanized antibody fragment that binds to different isoforms of VEGF. Approved by the FDA in June 2006, Lucentis is administered by injection into the eye.

Lucentis is descended from the same monoclonal antibody as Avastin (bevacizumab), another Genentech anti-angiogenic approved by the FDA in 2004 for colorectal cancer. Meanwhile, waiting for Lucentis approval, various groups were experimenting with Avastin for wet AMD. Dr. Philip Rosenfeld at the Bascom Palmer Eye Institute reported the results at the American Society of Retinal Specialists in 2005. Rosenfeld wrote in a later paper "The option of using Avastin for $17–$50 a dose is clearly more attractive than PDT at $1500 a treatment or Lucentis at $2000 a dose. Eventually, for us to know which treatment is better, a head-to-head clinical trial is necessary" (Rosenfeld, 2006).

"Six months later, hundreds of thousands of eyes in the US used Avastin." recalled Dr. Daniel Martin, professor of ophthalmology at Emory University Medical School and chair of the current NIH phase III clinical trials comparing Lucentis and Avastin. "It was remarkable, the closest thing to penicillin we had ever seen."

Regeneron Hopes for a Bit of Regeneration

A third player is now entering the Lucentis/Avastin scrimmage. Tarrytown, NY, based Regeneron (http://www.regn.com), a public company, has a compound for wet AMD, VEGF Trap-Eye, in phase III clinical trials. Regeneron's compound is designed to bind VEGF and the related Placental Growth Factor (PLGF). The study is expected to enroll approximately 1,200 patients in North America and will compare VEGF Trap-Eye to Lucentis. In 2006, Bayer Healthcare, LLC, struck a collaboration for VEGF Trap-Eye of $75 million up front and $245 million in milestone payments.

Regeneron's VEGF Trap-Eye approach involves attaching the binding portions of two different receptors to the Fc fragment of an antibody. This constructed molecule blocks signaling proteins from binding to receptors—impeding the formation of leaky blood vessels. According to Neil Stahl, Ph.D., senior vice president, research and development sciences, the VEGF Trap-Eye molecule is smaller than Avastin by ~50% but has ~2000-fold tighter binding than Avastin and 200 times that of Lucentis, affinities arrived at in the test tube but which need confirmation by this clinical trial. "In the closed compartment of the eye, you will get better blockage at lower drug levels." Stahl said. Regeneron is maximizing the half-life of the compound, an important consideration for patients who have to endure injections into their eyes. "A major goal of therapy is

to dry out the eye,'' Stahl said. ''We are also looking at reversing the size of the lesions.''

Banking on Eyes

Gregory Hageman, professor of ophthalmology at the University of Iowa, became interested in AMD in the late 1980s. ''The real issue is that there were no animal models.'' Hageman said. ''We decided to use human donor eyes to determine what these drusen were comprised of.'' Hageman accumulated 4000 pairs of eyes, 1000 pairs from AMD patients. He found the drusen contained proteins associated with the complement cascade, a biochemical cascade which helps clear pathogens from an organism, and hypothesized that AMD was caused by inflammation. In 2005, Hageman and several other groups found that AMD was associated with variants of the complement factor B and complement factor H genes. According to Hageman, these genetic variants account for up to 3/4 of cases of early AMD by producing defective proteins that cause immune system malfunction.

Hageman is cofounder and chief scientific officer of Optherion (http://www.optherion.com), which focuses on the earlier dry stage of AMD. Optherion is located in New Haven, CT, and at the University of Iowa. Instead of developing a systemic inflammation inhibitor, Optherion's approach will be to develop an augmented protein protective against AMD.

Orchestrated by biotech investor David Scheer, Optherion received $37 million in financing last year from a consortium of companies and venture capitalists. Optherion licensed its intellectual property from the University of Iowa Research Foundation, Yale, and the University of Pittsburgh on chromosome 10.

No direct inflammatory trigger for AMD has been found yet, although different groups are proposing infections with organisms like chlamydia. ''The thing about inflammation is that we don't know whether it is the cause or the result of the disease process.'' says Margaret DeAngelis, Ph.D., assistant professor of ophthalmology at Harvard Medical School and Massachusetts Eye and Ear Infirmary. Her group and others are studying the entire complement pathway to identify its precise role in AMD.

DeAngelis pointed out that while genes like complement factor H have variants associated with risk ''…there are a lot of people in the population walking around with these variants that don't have the disease.'' And what causes dry AMD to turn to wet AMD? ''We'd love to know,'' said DeAngelis. Part of the problem, according to DeAngelis, is lack of a good animal model, as the mouse has a retina but not a macula. ''The identification of CFH was a phenomenal stepping stone in beginning to develop a molecular biochemical profile for AMD risk'' said DeAngelis. ''From a chemical or biochemical standpoint it will be important to correlate our genetic findings at the protein level so that appropriate agonists and antagonists can be developed for treating this devastating form of blindness.''

Better Than a Poke in the Eye If They Can Get It to Work

San Diego-based TargeGen (http://www.targegen.com) hopes to dispense with the eye injections entirely and administer its wet macular degeneration, diabetic macular edema, and diabetic retinopathy treatment as eyedrops. The company's compound TG100801 is a benzotriazine inhibitor that targets the VEGF pathway. Specifically, their compound inhibits VEGFFr2 and members of the SRC kinase family. TargeGen has $36 million in D-round financing.

TG100801 was developed as a prodrug, an ester that is hydrolyzed by esterases to have active effects in the back of the eye. According to Richard Soll, Ph.D., vice president of research and development and chief scientific officer at TargeGen, the challenge was designing a drug for twice daily dosing that could be rapidly cleared from systemic circulation.

But TargeGen's Phase II clinical trials to look at the reduction of edema or leaks in the eye were halted when brown-colored microparticles of the compound appeared just below the cornea. The company is weighing its options: either to continue testing it at a 30× lower dose in an animal model, consider administering it through a device, or switch to another compound in the preclinical cupboard, TG100948, from a different chemical family. ''We will make a decision that will probably be made in context of a partner to develop or not,'' said Soll.

In another go-round, New Jersey-based Ophthotech (http://www.ophthotech.com) was inaugurated in 2007 with $36 million by former Eyetech execs to develop therapies for both dry and wet AMD. The company came with a dowry of three compounds: the first, E10030, an anti-PDGF aptamer, is entering a Phase I trial of up to 36 patients. E10030 is being tested in combination therapy with a VEGF-A inhibitor to see if it can roll back the angiogenesis of wet AMD. Additional compounds include ARC1905, a complement (anti-C5) inhibitor, and volociximab, an anti-angiogenesis monoclonal antibody-targeting $\alpha5\beta1$ integrin. ARC1905 inhibits C5, a trigger of inflammation, which is a part of the complement cascade.

Companies like TargeGen, Optherion, and Ophthotech are harbingers of new strategies such as easier delivery and combining drugs to knock off different parts of the problem. However, ''It is all extremely early,'' Martin said. ''I think the anti-VEGF therapies are likely to dominate for a while.''

REFERENCE

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