

Macular degeneration a key topic for retinal specialists

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WAILEA MAUI, Hawaii – The annual **Hawaiian Eye Meeting** was held here last week at the Grand Wailea Resort as specialists from three key ophthalmic specialties – cataract, refractive and retinal surgery – gathered to hear the latest clinical information and to enjoy the sunny and warm weather.

Physician attendance of about 700 was at a record level, despite the decline in the income in the refractive surgery community, as lucrative LASIK procedures have plunged about 40% in the second half of 2008 compared to 2007. It appeared that increased attendance was accounted for by the retinal specialists.

Age-related macular degeneration (AMD) is perhaps the most important disease treated by retinal physicians. It is a chronic, progressive disease of the macula, the central part of the retina and is the No. 1 cause of severe vision loss and blindness among those over age 50 in the developed world.

The FDA approval in mid-2006 of the **Genentech** (South San Francisco, California)-developed drug Lucentis literally revolutionized the treatment of AMD because, while this agent cannot halt the progression of the disease, in many patients it has somewhat miraculously improved their vision.

Lucentis inhibits vascular endothelial growth factor (VEGF), an important signaling protein involved in angiogenesis, the growth of blood vessels from pre-existing vasculature. In AMD, it is the growth of these new blood vessels (called neovascularization) that is a major culprit in vision loss.

Lucentis has been a tremendous commercial success in North America, with its sales in 2008 estimated at about \$850 million. However, it remains a very controversial drug, as its huge expense – approximately \$2,000 for the drug and another \$600 in associated office visit costs per injection – and the need to inject it frequently has been a burden to the budgets of seniors, ophthalmologists and to Medicare.

A sister drug to Lucentis is Avastin, an FDA-approved anti-VEGF drug which generated about \$2.7 billion of global revenue in 2008, almost all from the oncology market. Avastin is not FDA-approved for AMD but because it is chemically very similar to Lucentis and is also far cheaper (about \$50 per dose when used to treat AMD) its off-label use for AMD has surged in recent years.

The exact amount of ophthalmic Avastin usage is not known but it is clearly significant. During a session on the treatment of wet (advanced) AMD, moderator Carmen Puliafito, MD, dean at the Keck School of Medicine at the **University of Southern California** (Los Angeles), posed the question to the audience: "what is your preferred anti-VEGF drug?" Avastin was the preferred choice by 59% of the responders, vs. 38% for Lucentis. Similarly, only 15% of the physicians were using Lucentis exclusively, compared to 35% for Avastin.

In a talk on anti-VEGF agents, Jay Duker, MD, chairman of the department of ophthalmology at **Tufts New England School of Medicine** (Boston), said "there are lots of unanswered questions" in the treatment of wet AMD and that "the biggest question is the issue of Lucentis versus Avastin."

The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) sponsored by the National **Eye** Institute of the National Institutes of Health seeks to resolve the question of which drug is safer and more effective. CATT will enroll 1,200 patients with newly-diagnosed wet AMD. Results are not expected for at least two more years.

A very small trial comparing the two drugs head-to-head was presented here by Manju Subramanian, MD, assistant professor of ophthalmology at **Boston University School of Medicine**. Her 20-patient trial with three month follow-up showed a preliminary trend that Avastin patients fared better in vision improvement, though diagnostic measures – such as optical coherence tomography – of the health of the retina showed Lucentis performed somewhat better.

Noting that while the trial "is not statistically significant because of the small number of patients and limited follow-up," she indicated that more data would be forthcoming in the coming months.

Previous surveys have shown that on average Lucentis or Avastin is injected five or six times a year. This was corroborated by Anne Fung, MD, clinical professor at **California Pacific Medical Center** (San Francisco), who presented data from a 129-patient registry which began more than two years ago. It showed that an average of 5.4 anti-VEGF injections were used annually.

The significant cost of anti-VEGF therapy and the requirement that patients be seen very regularly imposes, in the words of Dr. Puliafito, "a therapeutic burden" for physicians and their patients. One potential and promising solution to this dilemma appears to be the use of ionizing radiation.

Elias Reichel, MD, director of the **New England Eye Center** (Boston), stated that radiation has several positive attributes – anti-angiogenic, anti-inflammatory and anti-fibrotic activities – and that "there would be a significant benefit if we could reduce the number of anti-VEGF injections."

Two privately-owned, venture capital-backed companies – **NeoVista** (Fremont, California) and **Oraya Therapeutics** (Newark, California) – are working in this area.

NeoVista has developed the Epi-Rad90 Ophthalmic System, in which a surgeon delivers focal strontium-90 beta radiation directly to the macula through a small incision in the outer layer of the **eye**.

Unlike external beam radiation, this novel system ensures delivery of a therapeutic dose of beta radiation to the wet AMD lesion and avoids any deleterious radiation exposure to other ocular structures such as the optic nerve and the lens.

The company is currently enrolling patients in its pivotal trial, dubbed the CNV Secondary to AMD Treated with Beta Radiation Epiretinal Therapy (CABERNET). The trial is being conducted at roughly 40 sites worldwide (20 in the U.S.) and is randomizing patients to either strontium-90 plus Lucentis or to Lucentis alone.

A total of 450 patients will enter the trial, 300 in the NeoVista arm and 150 in the Lucentis only arm. The primary endpoint is to determine which regimen will enable patients' vision to either improve the most or deteriorate the least.

Two other NeoVista studies are underway: ROSE, a feasibility study to determine the safety and efficacy of radiation therapy in those who do not have optimal response to treatment with anti-VEGF medication alone and the Macular EpiRetinal Brachytherapy In Treated Age Related Macular Degeneration Patients (MERITAGE) feasibility trial. The latter is now enrolling patients to will evaluate radiation therapy in wet AMD patients who require frequent persistent chronic therapy with anti-VEGF agents.

Oraya is developing the IRay System, designed to deliver a highly localized dose of low-energy X-Ray radiation non-invasively to the macula using a robotic positioning system, targeting algorithm and a device for **eye** stabilization. Its procedure can be performed quickly in the doctor's office under a topical anesthetic.

Oraya is currently enrolling patients into its feasibility trial outside the U.S., and some of its six-month data was presented at this **meeting**. The device has performed well with the impressive initial safety and efficacy data. A U.S. and European trial is expected to commence in the near future.

Commenting on the clinical progress from the two companies, Puliafito proclaimed that a combination approach using ionizing radiation and anti-VEGF agents is "very exciting and bears careful evaluation."

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