

CLINICAL NEWS

Ranibizumab Superior to Verteporfin in Head-to-Head Study

Data from a phase 3 clinical trial comparing ranibizumab (Lucentis; Genentech, San Francisco) to verteporfin (Visudyne photodynamic therapy [PDT]; Novartis, East Hanover, NJ) showed a mean change in visual acuity of 18 letters for patients treated with 0.3 mg ranibizumab and 21 letters for patients treated with 0.5 mg ranibizumab from study entry compared with those patients treated with PDT at 12 months.

In the first year of this 2-year Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study, patients treated with ranibizumab gained an average of 8.5 letters in the 0.3-mg dose group and 11 letters in the 0.5-mg dose group compared with patients treated with PDT, who lost an average of 9.5 letters, according to a news release. In

November 2005, Genentech announced that the phase 3 ANCHOR study met its primary efficacy endpoint of maintaining vision (defined as a loss of <5 letters in visual acuity) in patients with wet age-related macular degeneration (AMD). One-year data from the ANCHOR study were presented at a medical symposium held in New York and sponsored by the Manhattan Eye, Ear & Throat Hospital.

"[Ranibizumab] is the first investigational therapy that has shown improved vision, not just a slowing of vision loss, in patients with all types of wet AMD," said Peter K. Kaiser, MD, director, Clinical Research Center, The Cleveland Clinic Cole Eye Institute, who presented the data. Dr. Kaiser is a member of the *RETINA TODAY* editorial board. "As a result, physicians may be one step closer to being able to set a new expectation for the future treatment of this condition."

Vitrectomy Improves Vision in Select DME Patients

The benefits of vitrectomy as a treatment for patients with diabetic macular edema (DME) appear to be limited to those with evidence of macular traction, according to a report in the *British Journal of Ophthalmology*.

In an interview with Reuters Health, lead author D. Alistair H. Laidlaw, MD, FRCS, said, "Routine use of optical coherence tomography [OCT] in patients with diabetic macular edema can identify patients with signs of traction who may benefit from vitrectomy." Dr. Laidlaw is from St. Thomas' Hospital in London.

Dr. Laidlaw and colleagues sought to determine the preoperative demographic, clinical and OCT factors that might predict the visual and anatomical outcome at 1 year for patients undergoing vitrectomy with inner-limiting membrane peel for DME.

The study was a prospective, interventional case series of 33 patients with 1-year follow-up. Outcome measures were logMAR visual acuity and OCT macular thickness. "A priori explanatory variables included baseline presence of clinical and/or OCT signs suggesting macular traction, grade of

diabetic maculopathy, posterior vitreous detachment, fluorescein leakage and ischemia on angiography, presence of subretinal fluid, and preoperative indocyanine green use." Dr. Laidlaw wrote.

The central macular thickness improved from baseline by an average of 139 μ m, but there was a mean overall worsening in visual acuity at 1 year. Patients with macular traction, however, had about 1-line improvement in visual acuity compared with a 1-line deterioration in those who did not have evidence of macular traction.

Smoking Can Lead to Vision Loss or Blindness

AMD, affecting more than 1.65 million Americans over the age of 50 years, has no cure. Although several promising medications are currently being tested, those who have been diagnosed can only treat the symptoms.

Recent studies have shown that one way to reduce the risk of developing AMD is by not smoking. A study published in the *British Medical Journal* found that smokers were three to four times more likely to develop AMD than non-

smokers. And, nonsmokers living with smokers almost doubled their risk of developing AMD.

Former smokers who had quit for >20 years had the same risk level of those who had never smoked, according to the report. Smoking impairs the effects of antioxidants, which then damage the retina.

In a recent survey commissioned by AMD Alliance International (Toronto, Canada), only 32% of respondents who had heard of AMD were aware of the link between AMD and smoking. In addition to AMD, smoking has been linked to an increased prevalence of cataract, glaucoma and diabetic retinopathy.

"We've all known for years that smoking is bad for our health," said Daniel D. Garrett, senior vice president of Prevent Blindness America (Chicago). "But, some people may not know that besides causing cancers, smoking can also cause vision loss and eventually lead to blindness!"

In a related study, researchers from Bascom Palmer Eye Institute and Duke University have found that exposure to cigarette smoke, and in particular tar, triggers the formation of deposits and thickening in the retina that cause AMD.

The study by Ivan Suñer, MD, and colleagues, is the first to explore how cigarette smoke "generates biological changes in the eye that lead to vision loss" in AMD, according to a Duke news release.

Mice that were exposed to cigarette smoke or hydroquinone, the main ingredient in tar, developed subretinal deposits, thickening of Bruch's membrane and accumulation of deposits within Bruch's membrane.

"Understanding the molecular mechanism that causes these changes may lead to models that allow us to understand how macular degeneration is occurring. By understanding the biology, we may also be able to develop therapies to protect nonsmokers as well as smokers," Dr. Suñer said.

The study was published in *Investigative Ophthalmology & Visual Science*.

BUSINESS AND INDUSTRY NEWS

SiRNA Study Underway in Wet AMD; DME Study Initiated

The patient-dosing component of a phase 2 clinical program for small-interfering RNA therapy for the treatment of wet AMD has been completed, according to Acuity Pharmaceuticals (Philadelphia). The company

has also begun dosing patients in a pilot phase 2 trial of the agent, Cand5, in its second indication of DME.

The Cand5 Anti-VEGF RNAi Evaluation (CARE) is the first phase 2 efficacy trial for this therapy, which is based on gene-silencing technology. The study is a randomized, double-masked trial that includes three dose levels. In 4 months, 129 patients at 28 sites were enrolled; data and study results are expected by midyear.

RNAi Assessment of Cand5 in Diabetic Macular Edema (RACE) is a pilot phase 2 investigation of the safety and preliminary efficacy of Cand5 in patients with DME. It is a 48-patient, multicenter, double-masked, randomized study of three dose levels that is expected to be completed by the end of 2006.

Lawrence Singerman, MD, of Retina Associates of Cleveland is an investigator for both studies. "Investigators' recognition of the therapeutic potential of Acuity's novel gene-silencing drug facilitated achievement of our enrollment targets for this pioneering phase 2 study in wet AMD," he said. "Cand5 may also help preserve and enhance vision for the millions of individuals whose vision is threatened by the related condition of [DME], which is a growing problem worldwide and currently has few effective treatment options."

During the World Ophthalmology Congress in São Paulo, Brazil, Alexander Brucker, MD, said an important finding of the phase 1 safety trial was that no evidence of short-interfering RNA circulating in the blood was found. He added that mean visual acuity was stable at 6 weeks, and there was "very high stability over a period of 12 weeks."

"We have a very powerful anti-VEGF molecule," Dr. Brucker said. "It appears to have no systemic exposure and no significant ocular side effects."

Dr. Brucker, of the Scheie Eye Institute, University of Pennsylvania, said Acuity plans to begin phase 3 trials for each indication in the first half of 2007.

Inspire Discontinues Retinal Disease Drug Development Program

Inspire Pharmaceuticals (Durham, NC) has discontinued two phase 2 pilot clinical trials of denufosol tetrasodium intravitreal injection (INS37217) in patients with macular edema. The company said it has no plans

to conduct any further studies of denufosal for the treatment of retinal disease.

The two pilot trials of denufosal were initiated in the second and third quarters of 2005. The first trial was targeted to enroll 15 patients with persistent macular edema associated with uveitis. Data from this trial were reviewed following the treatment and evaluation of 12 patients. There were no significant safety or tolerability issues identified in the trial, however, the data did not demonstrate improvement in either reduction of retinal thickness or improvement in visual acuity. The second trial was targeted to enroll 15 patients with persistent macular edema following cataract surgery. No patients had yet enrolled in the second trial. Inspire has stopped enrollment in both trials, but will continue to follow the treated patients for safety for a period of 1 year, as specified in the protocol.

Ovine Hyaluronidase for Vitreous Hemorrhage Under European Review

The European Medicines Evaluations Agency has accepted Ista Pharmaceuticals' (Irvine, Calif) application for ovine hyaluronidase (Vitragan) for review. Known as Vitrase in the United States, the agent is used for the treatment of vitreous hemorrhage.

"Vitreous hemorrhage is a serious and debilitating eye condition that delays the diagnosis and treatment of the underlying problem, and, if left unchecked, can lead to blindness. Ista has accumulated a wealth of clinical data demonstrating that Vitrase can have a meaningful impact on reducing hemorrhage density and improving [BCVA] after only a single dose of treatment," said Vicente Anido Jr, PhD, president and CEO of Ista Pharmaceuticals.

FDA Grants Ranibizumab Six-Month Priority Review

The Food and Drug Administration (FDA) has accepted the Biologics License Application for the use of ranibizumab (Lucentis; Genentech, San Francisco) in the treatment of neovascular wet AMD, according to a Genentech news release.

The FDA grants priority review to products that are

considered to be potentially significant therapeutic advancements over existing approved therapies in the treatment diagnosis or prevention of a disease. The FDA has until the end of June to take action on the filing.

Preliminary results from the phase 3 Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) study showed that the improvements in the ranibizumab group at 1 year were maintained at year 2 as measured by visual acuity endpoints, while there was further deterioration of vision among patients in the control group.

PR Pharmaceuticals, OSI to Collaborate on Sustained-Release Pegaptanib

PR Pharmaceuticals (Fort Collins, Colo) announced an exclusive agreement with OSI Pharmaceuticals (Mellville, NY) to collaborate on the development of a sustained-release formulation of pegaptanib sodium injection (Macugen; OSI Eyetech/Pfizer, New York, NY). Pegaptanib, a novel treatment for neovascular AMD, will use PR Pharmaceuticals' proprietary ProPhase encapsulation technology.

Under the terms of the collaboration, PR Pharmaceuticals grants OSI Pharmaceuticals an exclusive license to use ProPhase technology with respect to pegaptanib in the treatment of eye diseases. The agreement gives OSI Pharmaceuticals and its development and marketing partner Pfizer access to a proprietary method for encapsulating pegaptanib for use in ophthalmology. PR Pharmaceuticals is responsible for developing the formulations and manufacturing the test article for non-clinical and clinical trials. OSI Pharmaceuticals, through its eye disease unit, is responsible for clinical development activities and has the right to manufacture and commercialize any resulting product.

Pegaptanib Receives European Marketing Clearance

The European Commission has granted OSI Pharmaceuticals and Pfizer approval to market pegap-

tanib for the treatment of neovascular AMD. According to a news release, pegaptanib has been proven to prevent and reduce vision loss in patients with neovascular AMD. It is the first treatment to target the underlying disease process and the first therapy approved in Europe for the treatment of all types of neovascular AMD, regardless of lesion subtype, size or baseline visual acuity.

"More than 50,000 patients have been treated with [pegaptanib] in the United States, and we are pleased that our partner Pfizer will make this important medicine available to patients in Europe," said David Guyer, MD, in a news release. He is executive vice president of OSI Pharmaceuticals and CEO of Eyetech, the OSI business team focused on eye disease. "In rigorous clinical studies, [pegaptanib] was effective and well-tolerated over 2 years, an important consideration for older patients treated for this chronic, progressive disease."

Pegaptanib has been approved by regulatory authorities in the United States, Canada, Brazil, Argentina, Peru, Pakistan and the Philippines, with filings submitted in 15 other countries including Australia, Switzerland and Mexico.

Neurotech Announces Publication of NT-501 Phase 1 Results

Neurotech (Lincoln, RI), announced that the findings from its phase 1 study of NT-501 for the treatment of retinitis pigmentosa (RP) have been published in the *Proceedings of the National Academy of Sciences*.

NT-501, the company's lead encapsulated cell technology (ECT) product, is an intraocular, polymer implant containing human retinal pigment epithelial cells genetically modified to secrete ciliary neurotrophic factor (CNTF). The implant is designed to continuously release CNTF directly in the eye to retinal tissue for sustained periods of time.

The open-label phase 1 study, conducted by lead investigator Paul A. Sieving, MD, PhD, of the National Eye Institute (NEI), was designed to assess the safety and tolerability of NT-501 in 10 patients with RP. In the study, two doses of CNTF were evaluated. NT-501 was implanted in one eye per patient and then removed after 6 months.

The results of the study showed that NT-501 can be safely implanted into the eye and was found to be well-

tolerated by patients. Although the study was not designed to assess clinical efficacy, three of seven patients with evaluable visual acuity experienced an improvement in visual acuity.

"This phase 1 study is a promising first step in evaluating the therapeutic potential of CNTF for diseases causing retinal and macular degeneration," said Dr. Sieving in a company news release. "In addition to safety and tolerability, I was encouraged by the apparent improvement in visual acuity scores of some patients."

Weng Tao, MD, PhD, chief scientific officer of Neurotech and a coauthor of the report said in a news release: "The results of the study demonstrate that CNTF can be safely delivered into the eye via ECT. This shows that ECT is a viable platform for the delivery of a variety of potential therapeutic factors to the eye for various retinal diseases."

"It is rewarding to see that our phase 1 results are published in a prestigious journal," said Ted Danse, president and CEO of Neurotech. "The company is committed to advancing NT-501 for retinal degenerative diseases with the continued support of the NEI and the Foundation Fighting Blindness (Owings Mills, MD). We will initiate two multicenter phase 2 clinical trials for RP in 2006."

Alcon Withdraws European Application for Anecortave Acetate

Alcon (Fort Worth, Texas) has withdrawn its application for marketing authorization for anecortave acetate (Retaane) in the European Union, according to a news release from the European Medicines Agency (EMA).

Alcon had submitted the application for the indication of treating exudative AMD in late 2004. At the time of the withdrawal, the drug was under review by the EMA's Committee for Medicinal Products for Human Use.

Alcon cited "research and development and marketing strategies" as reasons for the withdrawal, according to the EMA. Additional information about the drug and the current state of its scientific assessment will be made available later this month.

Retaane received an approvable letter from the FDA in May of 2005 after having been granted fast-track review status. The drug is approved for the treatment of AMD in Australia. ■