

CLINICAL NEWS

No Link Between Cataracts, AMD

According to data from the Age-Related Eye Disease Study (AREDS), there is no clear evidence of an association between cataract surgery and neovascular age-related macular degeneration (AMD). Speaking at the Association for Research in Vision and Ophthalmology (ARVO) 2006 Annual Meeting in Fort Lauderdale, Fla, Susan Bressler, MD, said, "Patients undergoing cataract surgery can probably be reassured that the surgery will not markedly increase their risk for progression to neovascular AMD." Dr. Bressler is director, Wilmer Photograph Reading Center, Wilmer Eye Institute, Johns Hopkins University School of Medicine.

According to the study, data from population-based studies have suggested that cataract surgery may result in an increased risk of developing advanced AMD. Dr. Bressler and colleagues investigated this potential relationship with the neovascular form of advanced AMD in data from AREDS. AREDS has many more cases of advanced AMD and cataract surgery than the published population-based studies, said Dr. Bressler.

Neovascular AMD was assessed annually from centrally graded stereoscopic fundus photographs. The investigators used four complementary analytic methods to assess the risk of neovascular AMD associated with cataract surgery. These were ordinary logistic regression, repeated measures logistic regression, cases (cataract surgery) versus matched controls and Cox proportional hazard with time-dependent covariates. Dr. Bressler and colleagues wrote that four methods were used because no single method is more clearly informative than the others, and each approach has both strengths and weaknesses compared with the other approaches. Analyses were for the right and left eyes separately and combined, using generalized estimating equations where possible. Covariate adjustments included age, smoking, gender, race, AREDS treatment and AMD status on a nine-point severity scale.

There were 1,704 cataract surgeries and 543 neovascular AMD events among 8,152 eyes with median follow-up of 9 years. Cataract surgery was not significantly associated with neovascular AMD in any of the analyses.

Bevacizumab Showed Efficacy, Safety for AMD

Bevacizumab (Avastin; Genetech, San Francisco) was associated with improvement in visual acuity, decreased retinal thickness and reduction in angiographic leakage in most patients in a study of 81 eyes with subfoveal AMD.

In this data presented at the ARVO meeting by Dante Pieramici, MD, codirector of the California Retina and Research Foundation in Santa Barbara, Calif, the majority of patients had previous treatment with photodynamic therapy (PDT) and/or pegaptanib (Macugen; OSI/Eyetech, New York, NY and Pfizer, New York, NY).

This was an interventional, consecutive, retrospective case series. Patients received 1.25 mg bevacizumab monthly until macular edema, subretinal fluid and/or pigment epithelial detachments resolved. Patients were evaluated by Snellen visual acuity, complete ophthalmic exam, fluorescein angiography and optical coherence tomography (OCT).

According to Dr. Pieramici, most patients had a reduc-

tion of retinal thickness by OCT beginning 1 week after injection. Four weeks following injection, 30 of 81 eyes demonstrated complete resolution of retinal edema, subretinal fluid and pigment epithelial detachments. At 1, 4, 8 and 12 weeks, the mean retinal thickness of the central 1 mm was decreased by 61, 92, 89 and 67 μm , respectively ($P < .0001$ for 1, 4 and 8 weeks and $P < .01$ at 12 weeks).

At 4 and 8 weeks, mean visual acuity improved from 20/200 to 20/125 ($P < .0001$). The median vision improved from 20/200 to 20/80- at 4 weeks and from 20/200 to 20/80 at 8 weeks, Dr. Pieramici reported.

The use of intravitreal bevacizumab for AMD treatment remains off-label, however, it is commonplace. According to Dr. Pieramici, it is being used in at least 70 centers in 12 countries and in thousands of patients. Many questions remain, he said, including the optimum dose. A phase 3 study needs to establish "true improvement" in visual acuity, he said.

The agent was well tolerated in this study, with one case of unusual uveitis in a patient who had four previous injections.

In a related presentation also at ARVO, Stephen Michels,

MD, professor of ophthalmology at the Medical University of Vienna, discussed systemic use of bevacizumab in AMD patients. Dr. Michels and colleagues compared the use of two regimens in a small group of patients in this prospective cohort study.

One group of 14 eyes (eight patients) received 5 mg/kg IV bevacizumab and one group of 12 eyes (seven patients) received 2.5 mg/kg of the agent. All patients received three infusions at 2-week intervals with 3-month follow-up. Patients were evaluated with regard to Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity, OCT and fluorescein angiography.

Dr. Michels said both groups showed a response to treatment after the first infusion. At day 7, the mean visual acuity increased from 56.3 letters at baseline to 60.4 letters in the 5 mg/kg group, and the mean central retinal thickness by OCT decreased by 83 μ m. The mean visual acuity increased from 59.8 letters to 65.5 letters and the mean OCT central retinal thickness decreased by 106 μ m in the 2.5 mg/kg group.

At the 3-month follow-up, visual acuity improved by eight letters compared with baseline in the 5 mg/kg group and by 11 letters in the 2.5 mg/kg group. A central retinal thickness reduction of 121 μ m in the 5 mg/kg group and 138 μ m in the 2.5 mg/kg group was noted. In all patients, Dr. Michels said that leakage documented by fluorescein angiography was either absent or reduced significantly by 3 months.

Initial follow-up showed comparable results with the two doses, he concluded. Further study is required to determine durability and long-term safety of the regimens. The doses in the study are equivalent to what a person would receive for the treatment of colorectal cancer, the Food and Drug Administration (FDA) approved indication for bevacizumab.

Two-Year MARINA Results: Ranibizumab Appears Safe

The use of ranibizumab (Lucentis; Genentech, San Francisco) appears safe in the treatment of AMD, according to 2-year results presented at ARVO. Joan Miller, MD, chair of the department of ophthalmology at Harvard Medical School, presented results from the Minimally Classic/occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trial.

The investigators found no imbalance in the number of deaths between the sham and ranibizumab groups, looking at 24-month outcomes, Dr. Miller said. Six deaths

occurred in sham-assigned patients in the second year of the study; five deaths occurred in the 0.3-mg ranibizumab group and six in the 0.5-mg ranibizumab group.

Among the 236 patients assigned sham treatment, nine had arterial thromboembolic events. Among the 238 patients in the low-dose treatment group, there were 11 events, and 11 occurred in the 239 patients assigned to the high-dose treatment. Dr. Miller said she believed the differences were not statistically significant. A companion study presented by Jeffrey Heier, MD, clinical instructor in ophthalmology at Harvard Medical School, showed that there was no drop off in efficacy after 2 years of treatment.

Triple Regimen Safe, Effective for AMD With Choroidal Neovascularization

A preliminary pilot study tested the effectiveness of combination therapy with high-dose intravitreal triamcinolone acetonide, verteporfin-based PDT (Visudyne; Novartis, East Hanover, NJ) and pegaptanib. Improvement was seen in visual acuity, resolution of subretinal fluid by OCT and reduction of fluorescein leakage, particularly when used as first-line therapy, said lead investigator J.M. Colina-Luquez, MD.

Dr. Colina-Luquez, from New England Retina Consultants in Hamden, Conn, and colleagues evaluated 22 eyes of 16 patients with active choroidal neovascularization (CNV) secondary to AMD. In this cohort, 13 had prior treatment with high-dose intravitreal triamcinolone acetonide and PDT with persistent CNV (prior treatment group). Nine eyes had newly diagnosed CNV with no prior treatment.

Follow-up ranged from 6 to 8 months; in the new treatment group, the mean acuity change was an improvement of 2.2 lines. In the prior treatment group, the mean change was an improvement of 0.7 lines. In the new treatment group, 33% of the eyes had an improvement of three or more lines and only 7.96% in the prior group, Dr. Colina-Luquez reported.

Additional studies are warranted to further evaluate this combination therapy, the investigators said.

No Link Between Vaccines for Anthrax and Optic Neuritis

The results from a postmarketing surveillance investiga-

RETINA NEWS

tion suggest that there is no association between optic neuritis and the anthrax, smallpox, hepatitis B or influenza vaccinations in the US military, whether these vaccines are administered alone or in combination.

The data were reported in the *Archives of Neurology*, by Daniel C. Payne, PhD, MSPH, and colleagues, from the Centers for Disease Control and Prevention. Case reports have suggested a possible association between optic neuritis and several different vaccines. To test the hypothesis, the investigators conducted a matched case-control study among US military personnel from Jan 1, 1998 through Dec. 31, 2003, using the Defense Medical Surveillance System. Statistical associations between vaccine exposures and optic neuritis within 6-, 12- and 18-week study intervals were estimated.

A total of 1,131 cases of optic neuritis and 3,393 controls were matched by sex, military component and deployment status.

There were no statistically significant associations between optic neuritis and anthrax vaccine for any of the three study intervals. There were no differences in optic neuritis risk when comparing those who received no dose, 1 and 2 doses of the vaccine. Similarly, there were no statistically significant associations between optic neuritis and smallpox, hepatitis B or influenza vaccines.

Possible Association Between Advanced AMD, Cognitive Impairment in Elderly

According to recent data from AREDS reported in the *Archives of Ophthalmology*, there may be an association between advanced AMD and visual acuity with cognitive impairment in older persons.

AREDS is an 11-center natural history study of AMD and age-related cataract. The AREDS Cognitive Function Battery was administered to 2,946 patients. The battery consists of six neuropsychological tests measuring performance in several cognitive domains. The Dunnett multiple comparison test was used to identify differences by AMD and visual acuity severity. The investigators used logistic regression to determine the relationship with cognitive impairment.

Mean scores of instruments in the AREDS Cognitive Function Battery declined with increased macular abnormalities and reduced visual acuity, according to the AREDS Writing Group. After adjustment for age, sex, race, educa-

tion, smoking status, diabetes, hypertension and depression, increased macular abnormalities (trend $P < .05$) reduced mean cognitive function scores as measured by the Modified Mini-Mental State Examination and the Wechsler Logical Memory Scale. Reduced vision was associated with reduced mean cognitive function scores as measured by the Modified Mini-Mental State Examination and letter and verbal fluency tasks.

Patients with vision worse than 20/40 in both eyes were more likely to be cognitively impaired (OR, 2.88 [95% CI, 1.75-4.76]) compared with patients who had a visual acuity of 20/40 or better in both eyes.

Statins May Improve Circulation in the Retina

According to a study in *Archives of Ophthalmology*, simvastatin induced an increase in blood velocity and blood flow in retinal arteries and veins, increased plasma nitrate/nitrite levels and decreased intraocular pressure (IOP).

The effect of statins on retinal circulation had not been studied, although previous research has shown that long-term use of the agents may reduce the risk of glaucoma, AMD and other diseases. Taiji Nagaoka, MD, PhD, from Asahikawa Medical College in Japan, and colleagues randomized 12 healthy men to a 20-mg dose of simvastatin or placebo for 7 days. Using laser Doppler velocimetry, they measured vessel diameter and blood velocity and calculated blood flow in retinal arteries and veins. The investigators also measured IOP and the plasma nitrate/nitrite levels.

They reported that daily administration of simvastatin for 7 days significantly increased blood velocity and blood flow in retinal arteries, but did not significantly change vessel diameter. The IOP significantly decreased at 90 minutes and at 7 days after administration of simvastatin. The agent also significantly increased plasma nitrate/nitrite levels.

Bone Marrow May Restore Cell Loss in AMD

Mice experiments conducted by University of Florida scientists have found evidence that the body naturally replenishes small amounts of cells in the eye needed for healthy vision.

According to a recent issue of *Investigative Ophthalmology & Visual Science*, retinal pigment epithelium (RPE)

may not be a nonrenewable resource after all. Damage to the RPE is present in AMD, which affects more than 1.75 million people in the United States. With evidence that the body indeed regenerates these cells in small amounts, scientists can focus on ways to accelerate natural healing processes to treat diseases, according to a University of Florida (UF) news release.

“What this tells us is that for problems such as [AMD], we should be able to harvest cells to help repair the damage,” said senior author Edward Scott, PhD, a professor of molecular genetics at the UF Shands Cancer Center and director of the Program in Stem Cell Biology and Regenerative Medicine at UF’s College of Medicine. “The question is whether we can do it in a patient.”

UF researchers believe it may be possible to grow new cells in the retina to replace those lost to injury or disease. They were able to detect that RPE cells appear to be naturally replenished in test animals by transplanting bone marrow cells from normal male mice into albino females with two different types of acute RPE injury.

Analysis showed that the cells that traveled to the injury site transformed into RPE and had male characteristics. They were also capable of inducing pigment.

“The dogma has been that we are born with a fixed amount of RPE, but there is growing evidence retinal progenitor cells exist in the adult,” said Lawrence Rizzolo, PhD, a Yale University associate professor of anatomy and experimental surgery and of ophthalmology and visual science. He was not involved in the research. “To derive cells or neuronal lineage from cells of bone marrow lineage is significant, if the finding stands up to the test of time. Compared with RPE transplantation, there are a lot of advantages if someone’s own bone marrow could supply the cells, because it is a ready source and the cells would not be rejected by the patient. Further, if bone-marrow progenitors circulating in the blood could be attracted to sites of disease, surgery could be avoided.”

BUSINESS AND INDUSTRY NEWS

Bromfenac B.I.D. Equivalent to Q.I.D. of Other Treatments

Patients treated with bromfenac ophthalmic solution 0.09% (Xibrom; Ista Pharmaceuticals, Irvine, Calif) achieved statistically significant improvements in both visual acuity and ETDRS letters gained, which were equivalent to diclofenac sodium ophthalmic solution 0.1%

(Voltaren; Novartis, East Hanover, NJ) and ketorolac tromethamine ophthalmic solution 0.5% (Acular; Allergan, Irvine, Calif) after 3 months of treatment.

Results of this physician-sponsored clinical trial were presented at ARVO. The trial was designed to compare the efficacy of bromfenac, a topical, b.i.d., nonsteroidal anti-inflammatory drug (NSAID) with two topical NSAIDs that were given q.i.d. for the treatment of acute pseudophakic cystoid macular edema (CME).

According to an Ista Pharmaceuticals news release, bromfenac is FDA approved for the treatment of ocular inflammation and reduction of pain following cataract surgery.

Under the study protocol, 52 patients with pseudophakic CME following cataract surgery were randomized to one of three regimens: bromfenac one drop b.i.d.; diclofenac one drop q.i.d.; or ketorolac one drop q.i.d.. Each patient was examined monthly for 3 months and measured for improvement in visual acuity using standardized ETDRS charts.

None of the ophthalmic NSAIDs are indicated for the prevention or treatment of CME.

“The reported clinical findings demonstrate that Xibrom’s enhanced potency and penetration lead to equivalent results with fewer applications each day, which may translate into a real benefit to patients from the financial and convenience perspectives,” said Lisa R. Grillone, PhD, vice president of clinical research at Ista Pharmaceuticals. “Other studies have shown that reducing the number of daily doses greatly increases treatment compliance with ophthalmic medications. We believe that improving compliance in this way can have a direct impact on clinical outcomes, particularly for treatments lasting several months or involving several different medications.”

For more information, visit www.istavision.com.

Pascal Photocoagulation Method Reported

Clinical experience of the first 550 eyes treated with the pattern scan laser (Pascal; Optimedica, Santa Clara, Calif) method of photocoagulation was reported by Harry Flynn J., MD, professor of ophthalmology at Bascom Palmer Eye Institute in Miami. Dr. Flynn reported results of 550 eyes from six clinical sites at the Retinal Physician Symposium 2006 on Current Concepts in Retinal Medicine at the Atlantis Resort on Paradise Island, Bahamas.

Dr. Flynn said that the Pascal method of photocoagu-

RETINA NEWS

lation resulted in an improvement in patient tolerance and reduced treatment time. Patients were treated at Bascom Palmer Eye Institute, Johns Hopkins University, the Jules Stein Eye Institute at UCLA, Stanford University, Associated Retinal Consultant in Detroit, and the Asociación Para Evitar La Ceguera in Mexico.

“These results clearly demonstrate the potential to make significant advances in the treatment of diabetic retinopathy and other retinal disorders with the Pascal Photocoagulator,” said David Mordaunt, CEO of OptiMedica. “Our commitment is to evolve ophthalmology through innovation — with Pascal we can now provide a superior physician and ultimately patient experience,” he added.

The Pascal method of photocoagulation is FDA approved to treat a variety of retinal conditions. For more information, visit www.optimedica.com.

Learning Retinal Implant Appears Feasible, Safe and Stable

Results of a limited clinical study related to Intelligent Medical Implants AG (Zug, Switzerland) early human trial were presented at The Eye and The Chip: World Congress on Artificial Vision in Detroit. The results demonstrated that Intelligent Medical Implants’ patented, first-generation Learning Retinal Implant enabled blind patients to see light — as well as simple patterns — via a wireless transmission of data and energy. According to a company news release, this represented the first time in the history of the development of artificial vision that completely wireless transmission of data and energy into an implant in the eye of long-time blind patients has resulted in pattern recognition.

The Learning Retinal Implant has been successfully implanted in four patients for up to 27 weeks to date (the first implantation occurred in late November 2005). Subsequent clinical testing of the Intelligent Medical Implants device with these patients began in January 2006 at the University of Hamburg Medical School, Germany, under principal investigator Gisbert Richard, MD, professor of ophthalmology.

“Our study concludes that it is possible to provoke pattern recognition by electrical stimulation,” said Dr. Richard. “The wireless data and energy transmission into the implant allowed totally unrestricted eye movement and is

therefore considered suitable as a long-term solution for blind [people].” Dr. Richard is chairman and head of the department of ophthalmology at the University Medical Center Hamburg-Eppendorf and General Secretary of the European Society of Retina Specialists (EURETINA).

“It is our intention that the Learning Retinal Implant System, along with rehabilitation, will facilitate patients’ recognition of objects by allowing them to identify their size, as well as their position, movements and shapes,” said Hans-Jürgen Tiedtke, CEO of IIP-Technologies, a subsidiary of Intelligent Medical Implants. “In short, a blind person, using our Learning Retinal Implant System, is expected to be able to move independently in an unfamiliar environment — thereby enabling him or her to lead an autonomous life. We have repeatedly said that development of a wireless visual prosthesis that can be implanted permanently with good results is surely the Holy Grail of artificial vision,” added Mr. Tiedtke.

This initial clinical indication focus is blind people with retinitis pigmentosa. For more information, visit www.intmedimplants.com.

Reneuron Group Announced Initial Data With Stem Cell Therapy

Joint research, led by Professors John Greenwood and Stephen Moss at the UCL Institute of Ophthalmology in London, showed expansion of human retinal progenitor cells with markers of photoreceptors over multiple population doublings. According to Reneuron (Surrey, UK), these progenitors showed an ability to engraft and protect the photoreceptor layer of the retina from degeneration in a retinal dystrophic model.

The research was funded by a Medical Research Council (UK) stem cells strategic research grant, and was presented at ARVO. To further its ReN003 retinal stem cell program, Reneuron also announced that it has entered into a collaborative research agreement with the Schepens Eye Research Institute at Harvard Medical School. The program aims to establish the key conditions for growing retinal stem cell lines that can be developed into a scalable, efficacious and safe therapy that utilizes Reneuron’s proprietary c-mycERTAM expansion technology.

The objective is to develop these stem cell lines to treat AMD, retinitis pigmentosa and diabetic retinopathy. For more information, please visit www.reneuron.com. ■