



What's Happening in AMD?
An answer based on presentations at AAO's
"Retina 2006: Emerging New Concepts"

Among the subspecialty events at the 2006 annual meeting of the American Academy of Ophthalmology (AAO), held jointly with the Asia Pacific Academy of Ophthalmology, was a two-day conference, *Retina 2006: Emerging New Concepts*. The conference was November 10-11, 2006, in Las Vegas. It was presented in conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin. Program directors were Emily Y. Chew, M.D., of the National Eye Institute of the National Institutes of Health, and John T. Thompson, M.D., of the Wilmer Eye Institute of The Johns Hopkins University.

The goal of *Retina 2006: Emerging New Concepts* was to update attendees about recent research and clinical findings relevant to diagnosis and management of vitreoretinal diseases. Age-related macular degeneration featured prominently. Among the topics were AMD risk factors and prevention, AMD and pharmacologic monotherapy, AMD combination therapy, other treatments for neovascular AMD, quality of life issues in patients with AMD, results of the Complications of AMD Prevention Trial (CAPT), and emerging developments in retinal imaging. What follows is a summary of the presentations.

A keynote presentation: Eye Care Dollars and Sense. Dr. Hugh Taylor delivered the 63rd Jackson Memorial Lecture, stressing that health planners and policy makers now have sufficient quantifiable data to give vision loss more significance on the health agenda. Dr. Taylor strongly asserted that governments must act now to create awareness of preventable blindness, provide access to available treatments, and provide more resources to essential research.

AMD Risk Factors and Prevention

- AMD is caused by a combination of genetic and environmental risks, some surely yet to be discovered. In most cases, the **genetic risk for AMD** is related to common polymorphisms in two genes, as presented at the meeting by Albert O. Edwards, M.D., Ph.D., and Rando Allikmets, Ph.D: in the complement factor H (CFH) gene a tyrosine is replaced with a histidine at position 402, increasing the risk of AMD by about five-fold; in the gene called LOC387715 an alanine is replaced with a serine, increasing the risk of AMD by about seven-fold. These risk rates are also driven by smoking, increasing one's risk even further. The variant in the CFH gene occurs in about 40 percent of Caucasians. The variant in the latter gene is found in about 30 percent of Caucasians. Other gene variants (in the complement factor B gene and the toll-like receptor 4 gene, for example) have been reported and account for a smaller number of cases of AMD. All in all, to date gene variants in the factor H, factor B, and LOC genes explain a large fraction of the genetic susceptibility to AMD.

Estimating the proportion of AMD caused by genetic variation is extremely difficult because of the influence that **environmental factors** such as smoking, systemic inflammation, and obesity have on AMD. Cigarette smoking

and body mass index both increase risk of AMD within the same genotypes. There also appears to be an interaction between obesity and genetic predisposition related to CFH.

- The role of the gene variants in predisposing Caucasians to AMD appears valid. As reported at the meeting by Susan B. Bressler, M.D., several studies suggest that variations in **CFH may predispose other ethnic groups, including Asians and Native Americans, to AMD but to a lesser extent.**

Prevalence rates for drusen, geographic atrophy, and choroidal neovascularization tend to be higher in whites than in blacks or Hispanics. The prevalence of advanced AMD in US adults is expected to increase by 59 percent by the year 2020, to nearly three million individuals.

- In the US population, overall **prevalence of drusen** of 125 micrometers in at least one eye is estimated at 6.12%, or roughly 7.3 million individuals, also according to Bressler. In 50 percent of cases, drusen are bilateral. According to a meta-analysis of the Eye Disease Research Prevalence Group, unilateral large drusen are associated with a six percent 5-year risk of progression to advanced AMD while bilateral large drusen are associated with a 26 percent 5-year risk of progression. The Eye Disease Research Prevalence Group—which included data from the Baltimore Eye Study, Barbados Eye Study, Beaver Dam Eye Study, Blue Mountain Eye Study, Rotterdam Eye Study, Salisbury Eye Evaluation Project, and the Melbourne Vision Impairment Project—shows that although all features of AMD are strongly age-related, there are no obvious gender differences.
- Patients with AMD often ask about their risk for more severe retinal disease. Based on the Age-Related Eye Disease Study (AREDS), using a repeated measures

logistic regression model incorporating generalized estimating equation methodology, a **5-step scale for estimating a person's five and 10 year risk of advanced AMD** in at least one eye was developed, as reported by Frederick L. Ferris, III, M.D.. The scale is based on the presence of drusen and pigment abnormalities. A score of 0 (no risk factors) represents a 0.5% risk; 1 factor, 3% risk; 2 factors, 12%; 3 factors, 25%; and 4 factors, 50%.

- A study looking at the 10-year effect of the **AREDS** supplement of high-dose antioxidants and zinc on progression to advanced AMD and moderate vision loss—among people at highest risk—showed that the effect of treatment did not diminish overtime. In other words, according to Emily Chew, M.D., study participants taking this AREDS supplement continued to have lower risk of progression to advanced AMD compared to subjects on placebo or other supplement combinations.
- **Geographic atrophy (GA)**, an advanced form of dry AMD, inevitably leads to vision loss. The risk is greatest the closer GA is to the fovea. As reported by Michael L. Klein, M.D., and previous studies, geographic atrophy appears to develop from large drusen that become confluent. This leads to focal hyperpigmentation and then hypopigmentation. Increased fundus autofluorescence and visual function abnormalities may precede geographic atrophy. GA is slowly progressive and may precede development of choroidal neovascularization. Eleven percent of people with bilateral GA develop neovascular AMD within four years.
- **Rheophoresis**, an extracorporeal blood filtration procedure, is an experimental procedure for reducing certain macromolecules in plasma. The rationale for its

use as a treatment for dry AMD is based on a potential to modify diffusion characteristics of Bruch's membrane, improve microcirculatory flow, and impact the complement cascade. A study called MIRA-1, by Occulogix, of rheophoresis in AMD failed to demonstrate a significant difference in visual acuity between a treatment and placebo group at 12 months. You may recall that when the MIRA reports were released, the company also stated that these poor results were attributable to "an anomalous response of the control group." The presentation at AAO appeared to elaborate on this, with Occulogix reporting that a gain of 0.8 lines was demonstrated when they removed from the 183 person trial any participants who had cataract surgery, cataract progression, YAG capsulotomy, fewer than four rheo treatments, central involvement of geographic atrophy or visual acuity greater or less than the inclusion criteria of between 20/32 and 20/125. A proposal for an additional Phase III clinical trial has been submitted by Occulogix to the FDA and this new trial is anticipated to be launched in first quarter 2007. This topic was presented by Ronald P. Danis, M.D.

AMD and Pharmacological Monotherapy

- Evidence indicates that the protein VEGF (vascular endothelial growth factor), and particularly its isoform VEGF-A, is a mediator of angiogenesis and vascular leakage in AMD. Among the newly developed VEGF inhibitors is **ranibizumab**, trade named Lucentis™, from Genentech. Ranibizumab is a high-affinity recombinant antigen binding fragment (Fab) that neutralizes all isoforms of VEGF-A. As reported by Napoleon Ferrara, M.D., its efficacy has been demonstrated in large randomized multicenter Phase III studies. Ranibizumab has been shown to slow down vision loss and even restore some vision in a significant

proportion of patients. The benefits were associated with a low rate of serious adverse events. Ranibizumab was approved in June 2006 by the FDA for the treatment of wet AMD.

- **Pegaptanib sodium** (trade name Macugen®), from OSI Pharmaceuticals and Pfizer), currently used in treatment of wet AMD, is an isoform-specific inhibitor of VEGF₁₆₅ and, therefore, an inhibitor of angiogenesis. (Macugen was the first drug therapy for AMD, approved in 2004 by the FDA.) VEGF₁₆₅ consists of two domains including a heparin-binding domain that distinguishes VEGF₁₆₅ from the other VEGF isoforms. The heparin binding domain is the primary target of Macugen. Injected in the eye, Macugen has been shown to stabilize vision for most AMD patients. Subjects are currently being recruited for a 54-week, open label, multicenter Phase IV clinical trial (called LEVEL) to test the safety and efficacy of Macugen injection once every six weeks as a maintenance therapy for patients who have received prior neovascular AMD treatment and experienced improvement in macular disease. This was reported by Lawrence J. Singerman, M.D.
- **VEGF** appears to have a role in **inflammation and in neuroprotection**, according to Anthony P. Adamis, M.D., recruiting leukocytes into the retinal vasculature and also conferring protection of neuronal cells during ischemia. Studies in rodents suggest a possible therapeutic impact of various isoforms of VEGF on retinal cells and also for conditions such as Parkinson's disease, stroke, and amyotrophic lateral sclerosis.
- **Patient reported outcome (PRO) measures** provide a valuable perspective for clinicians and researchers on what patients want and expect from treatment in order to maintain an acceptable quality of life. As such, the National Eye Institute developed the Visual Function

Questionnaire-25 (VFQ-25). Applied in two Phase III clinical trials (MARINA and ANCHOR) of ranibizumab (Lucentis™), VFQ-25 scores were significantly higher for near activities, distance activities, and vision-specific dependency among ranibizumab-treated subjects compared to those receiving sham injection or verteporfin PDT. Tom Chang, M.D., reported these findings.

- Various pharmacologic agents have been developed to inhibit VEGF for preventing intraocular neovascularization in AMD. This includes aptamers, soluble receptors (VEGF trap), siRNA (Acuity, SIRNA), and antibody and antibody fragments targeting VEGF. The **Phase III MARINA study** demonstrated the efficacy of one such compound, ranibizumab (Lucentis™). The primary efficacy endpoint of the MARINA study was the proportion of patients who at 12 months had lost fewer than 15 letters (approx. three lines) from baseline. As reported by Joan Miller, M.D., at 12 months 95 percent of patients receiving 0.3 mg or 0.5 mg ranibizumab injection had lost fewer than 15 letters in visual acuity compared to 62 percent of sham-injected subjects. In addition, many more drug-treated patients than sham-treated patients experienced a gain in visual acuity. The difference was evident as early as one month following the first injection.

AMD Combination Therapies and Others

- A general sense among ophthalmologists is that the most effective regimen for anti-VEGF therapy is one that provides steady dosing. A Phase IIIb clinical trial called PIER was conducted to determine **maintenance regimes for ranibizumab** (Lucentis™), comparing monthly with quarterly treatments. Reporting the results was Ursula Schmidt-Erfurth, M.D. The study

concluded that at 12 months the overall improvement rates in visual acuity were better with monthly compared to quarterly re-treatments.

- The **Phase III ANCHOR study** comparing ranibizumab (Lucentis™) to verteporfin (Visudyne®) photodynamic therapy (PDT) for maintaining visual acuity in patients with predominantly classic CNV lesions found that at 12 months ranibizumab was the superior treatment, reported Jeffrey S. Heier, M.D.. Even at one month the effect of ranibizumab on visual acuity was evident. Ranibizumab-treated patients on average continued to gain letters over the first year whereas the PDT group continued to decline in visual acuity.
- With **combination therapies** commonplace in oncology, researchers tested the same principle against AMD in patients with CNV. They treated over 100 patients with a single dose of triple therapy: **verteporfin PDT, the anti-inflammatory agent dexamethasone, and the anti-VEGF bevacizumab (Avastin®)**. Additional intravitreal injections of bevacizumab were provided as needed for retinal remodeling due to remaining edema. At 40 weeks, visual acuity was improved in most patients. The researchers believe there is much yet to be done in this area of research. This work was reported by Albert J. Augustin, M.D.
- The advantage of verteporfin PDT in neovascular AMD is its ability to eradicate existing CNV. PDT, however, may also cause VEGF up-regulation. To control vascular growth following verteporfin PDT therapy, researchers studied the effect of a **combination therapy using PDT and the anti-VEGF pegaptanib (Macugen®)**. Although they believe the idea has merit, based partly on preclinical studies in a murine

model of AMD, the study was terminated upon seeing no advantage of treatment compared to sham-treated subjects. They speculate that the order of dosing may be important or possibly more frequent injections of anti-VEGF. This work was reported Evangelos S. Gragoudas, M.D.

- The question of whether to use intravitreal injections of the anti-VEGF **bevacizumab (Avastin) or ranibizumab (Lucentis™)** to treat neovascular AMD is on the minds of many clinicians and patients. Although the two compounds are similar (differing in size and binding affinity) only Lucentis™ is FDA-approved for use in neovascular AMD. Avastin®, the less expensive of the two compounds, is approved only for metastatic colon cancer. In May 2005, clinicians began using Avastin® off-label for AMD treatment and, to date, thousands of patients worldwide have been treated successfully with no apparent increase in risk of endophthalmitis, ocular inflammation, or systemic complications. NEI recently announced a multicenter clinical trial (Comparison of Treatment Trial, CATT), to begin in 2007, for comparing the safety and efficacy of the two compounds. To date, reports of Avastin® treatment indicate an ability to improve visual acuity and halt neovascularization. This work was reported by Phillip J. Rosenfeld, M.D., Ph.D.
- Another approach being tested as an anti-VEGF therapy is **RNA interference**, described by John T. Thompson, M.D. The idea is to inhibit production of certain proteins by silencing genes that code for them, in this case for the protein VEGF. Although preclinical studies indicated an ability of the RNA interference compound (bevasiranib, Acuity Pharmaceuticals) to inhibit retinal neovascularization, intravitreal injection of bevasiranib at three different doses in a Phase II study—using visual acuity efficacy as the primary endpoint—did not

reach statistical significance. The researchers believe that ridding the tissues of VEGF before administering bevasiranib may be advantageous.

- The angiostatic compound **Retaane®** (Alcon), an anecortave acetate suspension, is also being tested as a suppressor of new blood vessel formation in AMD. Retaane® is delivered twice yearly by cannula to the juxtasclear space at the macula. Jason S. Slakter, M.D., Chairman of the Anecortave Acetate Clinical Study Group, described Retaane® as a possible risk reduction agent capable of preventing exudative AMD in people with dry AMD and as one of several therapeutic agents that could be effective in combination for treating exudative AMD. Over 2500 patients are currently enrolled at 116 sites in studies of Retaane®.
- Other treatments being tested for neovascular AMD include **VEGF trap, tyrosine kinase inhibitors, and squalamine**, described by Peter K. Kaiser, M.D. VEGF trap binds VEGF, preventing its interaction with its natural receptor. Early clinical studies with intravitreal administration of VEGF trap in exudative AMD patients show decrease in central retinal thickness and visual acuity improvement. Ninety-five percent of treated patients had stable or improved vision six weeks after a single treatment. Tyrosine kinase inhibitors target all VEGF receptors, preventing signal transduction. Preclinical studies are underway as are several Phase I clinical trials including one combining a tyrosine kinase inhibitor with verteporfin photodynamic therapy. Squalamine is an aminosterol isolated from the dogfish shark and capable of blocking the inflammatory pathway and VEGF. A Phase III clinical trial combining squalamine with verteporfin photodynamic therapy is currently enrolling patients. The FDA has granted fast track designation to squalamine.

- A 24-month study of a **telescopic implant** (IMT™) in one eye of over 200 patients with advanced AMD reveals that the device can improve visual acuity and quality of life, reported Paul Sternberg, Jr., M.D. Quality of life was measured using the NEI VFQ-25 scale. Researchers found that visual rehabilitation is critical to maximizing outcomes. Corneal endothelial cells loss and difficulty in viewing the retina through the device are two concerns. Researchers are hoping for FDA approval of the telescopic implant in 2007.
- **Macular translocation** as a therapy for AMD patients with severe vision loss was described by Cynthia Toth, M.D. In macular translocation the macula is moved to a position where subretinal tissue appears healthy. The complex surgery is proposed as a vision-salvaging treatment. The majority of patients on whom the surgery is performed experience significant improvement in visual acuity and maintain this improvement during the four year follow-up period. although the surgical complications can be devastating for vision and the eye. Recurrence of CNV following macular translocation was highest in smokers.
- The outcome of the **Complications of AMD Prevention Trial (CAPT)** was presented by Stuart Fine, M.D. CAPT was a prospective study assessing low intensity laser treatment of large drusen to prevent progression to more severe AMD. Over a thousand patients participated in the study. All began the study with large drusen and good visual acuity in both eyes. Each had treatment in one eye only. At five years, the researchers found no difference between the treated and untreated eyes in terms of incidence of late AMD, geographic atrophy, visual acuity, or reading ability. . In other words, this intervention was not successful in preventing complications of AMD.

- **OCT/SLO** was also discussed, by both Richard B. Rosen, M.D., and Yale L. Fisher, M.D. This imaging technology has the ability to simultaneously produce a confocal scanning laser ophthalmoscope (SLO) image and an optical coherence tomography (OCT) image. It is an extremely useful modality for detecting and quantifying fluid within and under the retina and the RPE and for identifying retinal pathology. As a user moves a scan line over an area of the retina, the technology displays coronal and cross-sectional scans of remarkably sharp resolution. Scanning is possible through varying depths of the tissues. The device also produces topographical maps and three-dimensional images that can be rotated and dissected for better viewing of pathologic features. As quantitative aspects of OCT/SLO become standardized, the technology is expected to become mainstream.
 - In a survey of AAO members concerning their **preferred AMD treatment**, Lucentis™ was ranked first, followed by PDT + intravitreal anti-VEGF treatment, then Avastin®, and then MPS-style laser photocoagulation. Physicians report finding that patients are becoming more comfortable with intravitreal therapies. The survey results were posted at the *Retina 2006: Emerging New Concepts* conference.
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