



ASSOCIATION FOR RESEARCH AND VISION IN OPHTHALMOLOGY 2007 ANNUAL MEETING

The 2007 meeting was held from May 6 to May 10 in Fort Lauderdale, Fla.

Two-Year ANCHOR Visual Acuity Changes Consistent With 1-Year Results

Analysis of the time course of visual acuity outcomes during the first year of Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) indicates that the mean visual acuity benefit of ranibizumab (Lucentis; Genentech, San Francisco) compared with photodynamic therapy (PDT) was evident after the first month of treatment, according to Jeffrey S. Heier, MD, from Ophthalmic Consultants of Boston. He said, however, that even neovascular age-related macular degeneration (AMD) patients who did not show this early benefit might respond later in the course of treatment.

ANCHOR is a phase 3, randomized, multicenter, double-masked trial, in which 423 patients were randomized 1:1:1 to ranibizumab 0.3 mg plus sham PDT, ranibizumab 0.5 mg plus sham PDT, or PDT plus sham ranibizumab injection. Ranibizumab (or sham) injection was administered monthly; PDT (or sham) was administered at study day 0 and then quarterly as needed.

Key visual outcomes in the primary analysis at 1 year were the proportion of patients losing <15 letters from baseline, the proportion gaining ≥ 15 letters from baseline, and mean change from baseline. These outcomes continued to be measured through the second year. Those key visual acuity endpoints have been previously presented and were quite robust, Dr. Heier said. The primary outcome of the prevention of moderate vision loss at 1 year was achieved in >90% of ranibizumab-treated patients versus roughly two-thirds of the PDT-treated patients, he said. At 2 years, these results were very well maintained.

"When we look at the percentage of patients who gained ≥ 3 lines, we see that it was 36% to 40% of the treated patients versus only 6% in the PDT group; at 2 years these results were maintained," Dr. Heier said. "When we look at mean change in vision, we see that the results that were achieved at 1 year—which was essentially a four-line difference between ranibizumab-treated patients and PDT-treated patients—were again maintained at 2 years, and there remained a four-line treatment difference between these groups."

With regard to safety findings, ocular adverse events were uncommon, and there was no overall imbalance in systemic safety events, he said.

The conclusion the investigators drew from ANCHOR is that the superiority of ranibizumab over PDT in visual out-

comes was evident very early, by a month, was increased over time, throughout 12 months, and then the benefit seen at 12 months was maintained over 24 months.

"As I look at this data—2 years of additional data not only from ANCHOR but from Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the treatment of Neovascular AMD (MARINA)—what I feel the most comfortable saying is that it serves to bolster our confidence in the consistency and the efficacy of this treatment."

Poor Agreement Found Between Snellen, ETDRS Charts

When researchers compared the visual acuity measurements obtained with the Snellen chart versus those obtained with the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart among eyes with and without AMD, they found poor agreement between the two methods.

"The poor agreement was more pronounced in patients with worse vision," according to William R. Freeman, MD, Professor and Director of the Jacobs Retina Center at the University of California at San Diego Shiley Eye Center, and colleagues.

The investigators randomly selected 104 patients (190 eyes) from a university-setting retina practice. Among the patient group, 80 (142 eyes) had some degree of AMD. The researchers measured visual acuity in each patient using standard procedure with both Snellen and the ETDRS charts in random order, according to the poster. Visual acuity was recorded in logMAR notations for statistical analysis.

The mean Snellen visual acuity overall was 0.78 logMAR (20/120), and the mean ETDRS visual acuity in the same eye was 0.54 logMAR (20/70). "In the low-vision group (<20/200), all patients with AMD, the average difference in number of lines was considerably larger than in the good vision range (>20/30)," Dr. Freeman said. According to Snellen, on average, 20/200 was 20/95 using ETDRS in the same eye, more than three lines difference. Snellen 20/30 was 20/25 with ETDRS in the same line, fewer than one line difference.

"ETDRS measurements yielded better visual acuity, particularly in participants with vision <20/200 [AMD patients]," the authors wrote. "We suggest taking these findings into consideration when comparing outcomes in clinical practices—which typically measure visual acuity using Snellen charts—with outcomes from clinical trials—which typically measure visual acuity using ETDRS charts."

PROTECT Study: Same Day Administration of Ranibizumab, Verteporfin

Same-day treatment with ranibizumab 0.5 mg and verteporfin PDT (Visudyne; Novartis, East Hanover, NJ) pro-



duced significant reductions in retinal thickness at 1 month, which were sustained over 9 months, according to results of the PROTECT Study.

Sebastian Wolf, MD, from the University of Bern, Bern Switzerland, reported that lesion area, greatest linear dimension, and leakage also declined slightly from baseline over 9 months.

PROTECT is an open-label, multicenter phase 2, 9-month study, in patients with predominantly classic (n=13) or occult (n=19), subfoveal choroidal neovascularization secondary to AMD, according to Dr. Wolf. Patients were randomized into three cohorts, with cohort treatment initiated sequentially at intervals of >30 days based on tolerance in the preceding cohort, according to the study abstract.

PDT with verteporfin was administered at baseline and then at months 3, 6, and 9 if leakage was present on fluorescein angiography (FA). Investigators also administered ranibizumab 0.5 mg at baseline within 1 hour after verteporfin therapy, and then monthly for 3 months, resulting in a total of four injections. Dr. Wolf explained that the exploratory endpoints included mean change from baseline in retinal thickness at months 1, 2, 3, 4, 6, and 9, as measured by optical coherence tomography (OCT), and lesion characteristics as measured by fundus photography and FA at months 3, 4, 6, and 9.

According to Dr. Wolf, 93% of patients at baseline or 26/28 patients with OCT measurements had intraretinal edema. During the course of the study, retinal thickness decreased by an average of 173 μm at month 1, from a baseline of 404 μm to 230 μm . "The decrease was maintained throughout the study with verteporfin PDT maintenance therapy as required, with a mean retinal thickness of 232 μm at month 9," Dr. Wolf said.

Fundus photography and FA measurements were made at baseline and at months 3, 4, 6, and 9. Mean lesion area (8.0 mm^2 to 7.3 mm^2), mean greatest linear dimension of CNV (3,367 μm to 3,230 μm), and FA leakage (8.2 mm^2 to 7.5 mm^2) were all reduced from baseline at month 9. During the 9-month exploratory study, 69% of patients required one initial verteporfin PDT, and only 9% required the maximum three verteporfin treatments, he said.

CAPT Data Do Not Support Protective Role of Statins in AMD

There is no consensus in the literature on whether statins offer protection against the progression of AMD, according to Colin A. McCannel, MD, from the Department of Ophthalmology, Mayo Clinic College of Medicine. He reported that the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) data do not support the concept of a strong protective effect of statins against

the development of CNV.

"Although CAPT statin users had a lower risk of geographic atrophy (GA), it was not a statistically significant change," Dr. McCannel said.

The CAPT enrolled 1,052 patients with ≥ 10 large drusen and visual acuity $\geq 20/40$ in each eye. For this analysis, patients who had their final CAPT visit after May 2005 were interviewed on their history of use of cholesterol-lowering drugs, including statins. According to the study abstract, trained readers identified CNV and endpoint GA (>1 Macular Photocoagulation Study [MPS] disc area of GA) based on review of fundus photos and FA taken at annual follow-up visits and when patients reported symptoms.

A Cox model using statin exposure as a time-dependent covariate for modeling person-specific risk was used to estimate relative risks (RRs) and 95% confidence intervals (CIs). Investigators repeated the analysis on the subset of patients with no change in statin use during their time at risk in CAPT.

Among the 744 patients who provided a medication use history, 86 started statins before enrollment in CAPT, 28 started in the same year, and 182 starting during the study. There were 448 patients who said they never used statins. CNV developed in 176 eyes, and GA developed in 80 eyes.

"Including statin use as a time-dependent covariate in the survival analysis yielded an RR for CNV of 1.20 (CI, 0.86-1.68)," Dr. McCannel said. "When the analysis was restricted to those with no change in statin use, the RR for CNV was 1.13 (CI, 0.69-1.88)." The RR for GA was 0.62 (CI, 0.36-1.06) when statin use was included as a time-dependent covariate and was 0.41 (CI, 0.15-1.14) in the restricted group. Adjusting for other risk factors had little impact on the results.

Data Suggest Improvement in Macular Edema With Ranibizumab

Preliminary data from a study of ranibizumab for macular edema due to retinal vein occlusions reveal that three intravitreal injections of ranibizumab have been well-tolerated. Regardless of dose, these data suggest overall improvements in visual acuity and foveal thickness, according to data presented by Peter A. Campochiaro, MD, and colleagues from the Wilmer Research Group.

"It will be important to determine if there are differences between the treatment groups," Dr. Campochiaro said.

Patients with macular edema due to central (CRVO, n=20) or branch retinal vein occlusion (BRVO, n=20) are being randomized 1:1 to receive three monthly injections of 0.5 mg or 0.3 mg of ranibizumab. The primary outcome being evaluated is change in visual acuity from baseline at 3 months. Secondary outcomes are change in visual acuity



UPDATE FROM 2007 ARVO

from baseline at 0.25, 1, 2, 4 and 6 months, and change in central 1-mm foveal thickness at all of the time points.

Twelve patients with BRVO and 14 with CRVO have been randomized. Interim results without regard to treatment assignment can be seen in Table 1 below:

TABLE. 1 BRVO AND CRVO RESULTS

BRVO		Visual Acuity (letters)		Foveal Thickness (µm)	
Time (mos)	n	Mean	Median	Mean	Median
Baseline	12	20.25	21	513.67	508
0.25	12	28.00	32	286.25	286
1	10	33.20	34	254.50	266
2	10	32.75	34	227.38	231
3	4	35.50	37	198.50	208
CRVO		Visual Acuity (letters)		Foveal Thickness (µm)	
Time (mos)	n	Mean	Median	Mean	Median
Baseline	14	16.07	13	526.71	504
0.25	14	23.21	19	315.21	271
1	13	23.69	20	360.85	254
2	11	26.36	21	311.55	247
3	6	24.33	21	327.67	272

Two-Year FOCUS Revealed Reduced Vision Loss With Ranibizumab Plus PDT

At 24 months, combination therapy with ranibizumab and verteporfin PDT, reduced vision loss of >15 letters compared to verteporfin PDT alone. The combined treatment also increased mean visual acuity over baseline, reduced progression to 20/200, and the need for PDT retreatment, according to Paolo Lanzetta, MD, from the Department of Ophthalmology, University of Udine in Italy.

Dr. Lanzetta presented results of the RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS) study, which compared the safety and efficacy of monthly intravitreal injections of ranibizumab combined with verteporfin PDT and PDT alone in patients with subfoveal, predominantly classic CNV secondary to AMD.

FOCUS is a phase 1/2, multicenter, randomized, single-masked, controlled study, and patients were randomized 2:1 to receive either monthly ranibizumab 0.5-mg (n=106) or sham (n=56), according to the abstract. Verteporfin PDT was initially performed 7 days before ranibizumab or sham and then every 3 months as needed in both arms.

At 24 months, 87.5% of combination-treated patients had lost <15 letters, compared to 75% of the PDT-only arm ($P=.04$), Dr. Lanzetta said. Mean visual acuity improved in the combination-treated group by 4.6 letters

over baseline, compared to a loss of 7.8 letters in the PDT-only group ($P<.0001$).

“The visual acuity benefit was seen as early as 7 days and was maintained throughout the study,” he said. “In addition, 24.8% of combination-treated patients

improved mean [visual acuity] by >15 letters, compared with 7.1% in the control group ($P=.006$), and only 30.5% of patients progressed to 20/200 vision with combination, compared to 50% with PDT alone ($P=.006$).”

On average, after initial PDT, a mean 0.4 additional verteporfin treatments were required in the combination group, compared to an additional 3.0 verteporfin treatments in the PDT-only group. Investigators identified a higher incidence of intraocular inflammation at 12 months. This was significantly reduced following a protocol amendment changing ranibizumab from a lyophilized to the liquid formulation, and increasing the interval between the two treatments in the combination arm to 28 days.

Drusen Analysis May Help Predict CNV Occurrence

Maria Palaïou, MD, from the University of Pittsburgh, reported that drusen analysis of baseline characteristics may help predict the likelihood of a CNV event occurring in an eye. “The presence or absence of pigment in the macula was a consistent risk factor,” she said.

The investigators pooled 522 participants aged >50 years from the Age-Related Eye Disease Study (AREDS) trial with the Prophylactic Treatment of AMD (PTAMD) participants at the Pittsburgh site. All patients were followed photographically for at least three visits over a 2-year period (baseline, 12 months, and 24 months), according to the abstract.

A trained technician assessed digitized fundus images for drusen using the Drusen Analyzer (Iridex, Mountain View, CA) program, which quantitates drusen parameters. Readers confirmed CNV events on FA for the respective trials. The following parameters were evaluated for each study: total drusen area in the central 1,000 µm of the macula, drusen area in the central 3,000 µm, the presence of atrophy within 1,000 µm, the presence of atrophy within 3,000 µm, the presence of pigment within 1,000 µm and the presence of pigment within 3,000 µm. The researchers pooled those parameters from both studies to create a larger population.

“We fitted a mixed effect longitudinal model to drusen area and a mixed effect model with a random intercept



to the event data," she said.

At baseline, statistically significant factors ($P < .05$) for predicting the occurrence of an event within the studies were total drusen area within the central 1,000 μm diameter field and the presence of pigment within the central of 3,000 μm . "The study assignment was also a significant factor," Dr. Palaiou said.

The correlation coefficient between the occurrence of an event and the predicted probability of occurrence was 0.18 for the model, which incorporated drusen area within 1,000 μm and the study assignment. The presence of pigment at 3,000 μm adds 0.04 to the correlation coefficient when it was included in the model. Using a full model that includes age, study assignment, drusen area within the central 1,000 μm and the presence or absence of pigment, an increase in drusen area within the central 1,000 μm from 0.1 mm^2 to 0.1064 mm^2 increased the odds of an event occurring by about 42%.

"Note that a single druse 125 μm in diameter has an area of 0.012 mm^2 ," Dr. Palaiou said. "Having pigment alone increased the odds for an event by 313% in this model!"

The presence or absence of pigment in the macula was a consistent risk factor, the investigators concluded. The odds of an event occurring in the PTAMD study subset was 35 times that of an event occurring for the AREDS study, but PTAMD participants were all selected because of their higher risk characteristics, she pointed out.

Seven Year Daily Folic Acid Plus B-Vitamins May Reduce AMD in Women With CVD

William Gerard Christen Jr, MD, Associate Professor of Medicine, Harvard Medical School presented data from the Women's Antioxidant and Folic Acid Cardiovascular Study (WACS). He and colleagues found that, in this large cohort of women with cardiovascular disease (CVD), 7 years of daily supplementation with folic acid/ B_6/B_{12} reduced the risk of AMD.

WACS was a randomized, double-blind, placebo-controlled trial of antioxidant vitamins and a folic acid/vitamin B_6 /vitamin B_{12} combination in the prevention of CVD events among female health professionals aged ≥ 40 years with pre-existing CVD or ≥ 3 CVD risk factors.

According to the abstract, a total of 8,171 women were randomized to vitamin E, vitamin C, beta carotene, or placebo. Of this group, 5,442 women were also subsequently randomized to folic acid (2.5 mg/d), vitamin B_6 (50 mg/d), and vitamin B_{12} (1 mg/d), or placebo; 5,205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis.

In this study, the main outcome measures were confirmed AMD, defined as a self-report supported by medical record

evidence of an initial diagnosis subsequent to randomization, and AMD with vision loss, defined as confirmed AMD with vision $\leq 20/30$ attributable to this condition.

The average treatment and follow-up was 7.3 years, and a total of 137 cases of AMD were documented. There were 69 cases responsible for vision loss $\leq 20/30$. For the endpoint of confirmed AMD, Dr. Christen said, there were 55 cases in the folic acid/ B_6/B_{12} group and 82 in the placebo group [RR, 0.66; 95% CI, 0.47-0.93; $P = .02$].

For AMD with vision loss, there were 26 cases in the folic acid/ B_6/B_{12} group and 43 in the placebo group (RR, 0.60; 95% CI, 0.37-0.98; $P = .04$).

Encouraging Results of VEGF Trap-Eye in Neovascular AMD

In a phase 2 neovascular AMD trial, data were presented from a pre-planned interim analysis of the first 78 patients who completed 12 weeks of the study. The randomized, multicenter trial involves 150 patients randomized to five groups and treated with the VEGF Trap-Eye (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) in one eye. Two groups received either 0.5 mg or 2.0 mg of VEGF Trap-Eye administered every 4 weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye. Patients were monitored for safety, retinal thickness, and visual acuity over 12 weeks, according to a news release.

The VEGF Trap-Eye investigation met its primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline (all groups combined, decrease of 135 μm , $P < .0001$). Mean change in visual acuity, a key secondary endpoint of the study, also demonstrated a statistically significant improvement (all groups combined, increase of 5.9 letters, $P < .0001$).

There were no drug-related serious adverse events, and treatment with the VEGF Trap-Eye was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

The Phase 2 neovascular AMD study is now fully enrolled and results for all patients will be presented at a future scientific meeting.

Encouraging results were also presented from a phase 1 study of VEGF Trap-Eye in diabetic macular edema (DME). In this open-label safety study, VEGF Trap-Eye was administered as a single 4.0 mg intravitreal injection to five patients with longstanding diabetes and multiple prior treatments for DME. The single injection resulted in a marked decrease in mean central retinal thickness and mean macular volume throughout the 6 week observation period. The VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events. Adverse events were mostly related to the injection procedure. ■