ARVO RECAP

As a service to our readers, we are providing a recap of the major presentations at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Orlando, Florida, held May 3 to May 8, 2014. This feature is not intended to be all-inclusive; but rather reflects our editor's picks as some of the top presentations at the meeting.

VISTA: 52-Week Results Sustained at 100 Weeks

Benefits gained through 52 weeks of study in the VISTA trial were sustained at 100 weeks, according to David M. Brown, MD.[1,2]

VISTA was a double-masked, phase 3 trial assessing the safety and efficacy of 2.0-mg intravitreal aflibercept (Eylea, Regeneron) injections administered every 4 weeks (2q4) or 8 weeks (2q8, after 5 initial monthly loading doses) versus laser photocoagulation in patients with diabetic macular edema (DME). The study was conducted in multiple locations in North America. Data analysis of 100-week results from VIVID, a companion trial being conducted at multiple European and Asian sites, is ongoing, according to Dr. Brown.

At 100 weeks, patients in the 2q4 group in VISTA had a BCVA improvement of 11.5 letters from baseline (a loss of 1.0 letters from week 52) and 11.1 letters in the 2q8 group (a gain of 0.4 letters from week 52). Patients in the laser photocoagulation group had a mean BCVA improvement of 0.9 letters from baseline (a gain of 0.7 letters from week 52). Mean BCVA gain from baseline was the primary efficacy endpoint.

Arterial thromboembolic events occurred in 8.39% (13 of 155) of patients in the 2q4 group, 7.24% (11 of 152) of the 2q8 group, and 5.84% (9 of 154) of the laser photocoagulation group.

According to the data from an analysis at 52 weeks, there was a significant gain in mean BCVA from baseline in the aflibercept groups versus the laser photocoagulation groups in VISTA. The 2q4 group had a 12.5-letter gain, the 2q8 group had a 10.7-letter gain, and the laser group had a 0.2-letter gain (P <.0001).

In VISTA, 41.6% of the patients in the 2q4 group and 31.1% of the patients in the 2q8 gained ≥15 letters from baseline versus 7.8% of patients who received laser photocoagulation (P < .0001) through 52 weeks. The proportion of patients who lost 15 letters or more in the 2q4, 2q8, and laser groups, respectively was 0.6%, 0.7%, and 9.1% in VISTA.

Mean reduction in central retinal thickness at week 52 in VISTA for the 2q4 and 2q8 groups versus laser was 185.9 µm and 183.1 µm versus 73.3 µm (P < .0001).

The 100-week VISTA results reported were consistent with a press release from the company issued in February 2014.[3]

1. Brown DM. Intravitreal aflibercept injection (IAI) for diabetic macular edema (DME): Primary and additional endpoint results from the 12-month phase 3 VISTA-DME and VIVID-DME studies. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.
2. Brown DM. Intravitreal aflibercept injection (IAI) for diabetic macular edema (DME): Primary and additional endpoint results from the 100-week phase 3 VISTA-DME and VIVID-DME studies. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.
3. Two-year results from phase 3 VISTA trial of Eylea (aflibercept) injection for the treatment of diabetic macular edema show sustained improvement in vision [press release]. Tarrytown, NY; Regeneron; February 10, 2014.

Prior Anti-VEGF Use Did Not Affect Outcomes in VIVID/VISTA

Patients who had previously received anti-VEGF therapy for DME had similar outcomes as treatment-naïve patients in the VIVID and VISTA trials, according to Quan Dong Nguyen, MD.[1]

In VIVID, chiefly conducted outside of the United States, 6% to 10% of patients had prior anti-VEGF therapy; in VISTA, which was conducted in the United States, 46% to 47% of patients had prior anti-VEGF therapy.

The mean BCVA improvement from baseline to week 52 for the 2q4 and 2q8 groups, respectively, was 10.8 and 9.8 letters in the total patient population. Patients in those groups with prior anti-VEGF therapy had improvements of 11.8 letters and 11.7 letters; patients in those groups without prior anti-VEGF therapy had improvements of 10.5 letters and 9.2 letters.

Anatomic improvements showed a similar pattern, Dr. Nguyen reported. The mean reduction in central retinal thickness for the overall population was 132.7 µm for the 2q4 group and 127.1 µm for the 2q8 group. Patients who had received prior anti-VEGF therapy had a reduction in central retinal thickness of 108.9 µm and 116.5 µm in the 2q4 group and the 2q8 group, respectively; patients who were treatment naïve had reductions of 142.3 µm and 131.8 µm, respectively.

1. Nguyen QD. Impact of prior therapy of diabetic macular edema (DME) on visual and anatomic outcomes following treatment with intravitreal aflibercept: Results from the phase 3 VISTA-DME and VIVID-DME studies. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Age, Subretinal Fluid Predicted BCVA Improvement in RISE/RIDE

Younger age, the presence of subretinal fluid, and baseline BCVA were among the predictors of a gain of 15 letters or more after treatment with ranibizumab (Lucentis, Genentech) for DME in the RISE and RIDE trials, according to Raafay Sophie, MD.[1]

Young age, the presence of subretinal fluid, and good BCVA at baseline were predictive of BCVA of 20/40 or more, and poor baseline BCVA was predictive of BCVA less than 20/100. Panretinal photocoagulation administered prior to or during the study predicted BCVA less than 20/40. Low central foveal thickness, subretinal fluid, and small versus large cysts predicted central foveal thickness of 250 µm or less.

For sham-treated patients, young age and low baseline central foveal thickness predicted a gain of 15 letters or more; poor baseline BCVA was associated with BCVA gain of 15 letters or less. Young age and low baseline central foveal thickness predicted a final BCVA of at least 20/40; good baseline BCVA was associated with final BCVA greater than 20/40. Renal disease predicted BCVA less than 20/40.

Several baseline factors in sham-treated patients predicted a final central foveal thickness of 250 µm or less, including low central foveal thickness at baseline, the presence of subretinal fluid, small versus large cysts, poor baselines BCVA, panretinal photocoagulation administered prior to or during the study, and statin use.

1. Sophie R, Lu N, Campochiaro PA. Baseline predictors of functional outcomes in patients with diabetic macular edema (DME) in the RISE and RIDE trials. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Treat-and-Extend Protocol Maintained VA Gains in RISE/RIDE Extension Trial

Visual acuity gains from monthly ranibizumab treatment in RISE and RIDE were maintained with less-than-monthly treatment in an open-label extension trial, reported Allen C. Ho, MD.[1]

Patients who received 24 months of sham treatment in RISE and RIDE were eligible to crossover to monthly 0.5 mg ranibizumab treatments. After 36 months, all patients received 0.5 mg ranibizumab regardless of prior randomization. Patients who did not meet prespecified treatment criteria could be extended from 30 days between treatments to 60 days or 90 days.

Visual acuity gains achieved after 36 or 12 months of monthly ranibizumab dosing were maintained with less-than-monthly dosing, according to the study. Patients randomized to sham therapy during the core trials never achieved the same visual acuity gains as those who received 0.3 mg or 0.5 mg ranibizumab. Patients in the extension trial had an average of 4.5 injections during 14.1 months of follow-up. Fewer than 10% of patients continued with monthly ranibizumab treatments and approximately 25% of patients did not require additional ranibizumab to maintain visual acuity. Visual acuity results were maintained in patients who received ranibizumab treatment in the extension trial.

Adverse events in the extension trial were similar to the known safety profile of ranibizumab as observed in the core trials.

"The RISE and RIDE extension studies demonstrate the long-term durability of ranibizumab's efficacy in DME," Dr. Ho reported. "In those requiring further treatment, these data demonstrate that less-than-monthly treatment can be sufficient to maintain vision for the majority of patients."

1. Ho AC, Zhang J, Ehrlich JS. Ranibizumab for diabetic macular edema: Long-term open-label extension of the phase III RIDE and RISE trials. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Treat-and-Extend Ranibizumab Regimens Noninferior to As-Needed Treatment in DME

Treat-and-extend (TE) regimens of ranibizumab were shown to be noninferior to as-needed regimens of treatment of DME at 24 months in the RETAIN trail, said Christian Pruente, MD.[1]

In the RETAIN trail, patients with DME and poor visual acuity were randomized to 3 groups: TE ranibizumab with laser photocoagulation (n = 121), TE ranibizumab (n = 128), and as-needed ranibizumab (n = 123). Based on mean change in BCVA from 1 month through 12 months, the TE ranibizumab with laser group and the TE ranibizumab group were noninferior to the as-needed ranibizumab group (+5.1 letters, +6.1 letters, and +6.2 letters, respectively; $P < .0001$). Mean change in BCVA from baseline at month 24 was similar across all 3 groups (+8.3 letters, +6.5 letters, and +8.1 letters, respectively). The number of visits for TE patient groups was approximately 40% lower than that of the as-needed group; about 70% of TE patients had monitoring intervals of 2 months or more. There were no new safety findings over 24 months reported in the analysis.

These findings "demonstrate that TE ranibizumab regimens were noninferior to as-needed regimens in the

RETAIN patients with mild to moderate vision loss," Dr. Pruente said. "The TE regimens led to a potential reduction in the number of patient visits based on individual patient response."

1. Pruente C. Efficacy and safety of ranibizumab in two treat-and-extend versus pro-re-nata regimes in patients with visual impairment due to diabetic macular edema: 24-month results of RETAIN study. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Dexamethasone Implant Reduced Central Retinal Thickness, Macular Volume

Patients with DME who received a dexamethasone intravitreal implant (Ozurdex, Allergan) had reductions in central retinal thickness, macular volume, and area of macular thickening in 2 trials (NCT00168337 and NCT00168389), according to Ronald P. Danis, MD. [1]

In the 2 identical multicenter, randomized, sham-controlled phase 3 trials, patients with DME, BCVA between 34 and 68 letters, and central retinal thickness (CRT) of at least 300 µm were randomized to receive either a 0.7-mg or 0.35-mg dexamethasone implant, or sham.

At all study time points, patients in the dexamethasone implant groups had reduced CRT (-117.3 µm and -127.8 µm in the 0.7-mg and 0.35-mg dexamethasone implant groups, respectively; mean change from baseline to study end; both $P < .001$ vs sham). There were similar associations in macular volume (-1.06 mm^3 and -1.14 mm^3 in the 0.7-mg and 0.35-mg dexamethasone implant groups, respectively; mean change from baseline to study end; both $P < .001$ vs sham). Patients treated with a dexamethasone implant had reduced disc areas of macular thickening on color photographs (-2.753 and -2.931 in the 0.7-mg and 0.35-mg implant groups; both $P < .001$).

Patients in the dexamethasone implant groups had improvement in macular edema (20.4% and 22.4% in the 0.7-mg and 0.35-mg groups vs 12.4% in the sham group; $P < .05$). The 0.7-mg dexamethasone implant reduced the risk in time to 2-step worsening in Diabetic Retinopathy Severity Score by 44% over the study period ($P = .03$ vs sham).

Reporting on the same collection of pooled data, Rubens Belfort Jr, MD, reported that rates of cataract-related adverse events in phakic eyes were 67.9% for the 0.7-mg dexamethasone implant group, 64.1% for the 0.35-mg dexamethasone implant group, and 20.4% for the sham group.[2] Increases in intraocular pressure were usually controlled with medication or no therapy and only 1 (0.3%) patient treated with the 0.7 mg implant and 1 (0.3%) patient treated with the 0.35 mg implant underwent glaucoma incisional surgery for steroid-induced intraocular pressure increases.

1. Danis RP, Sadda SR, Cui H, et al. Anatomic outcomes with dexamethasone intravitreal implant in diabetic macular edema: a pooled analysis of two randomized phase 3 trials. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.
2. Belfort R Jr, Boyer DS, Yoon YH, et al. Three year, randomized, sham-controlled, phase III study of dexamethasone intravitreal implant in patients with diabetic macular edema. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

No Difference in Visual Acuity in Study of Bevacizumab and Dexamethasone Implant

There was no significant difference in final visual acuity or CMT in a head-to-head comparison of bevacizumab (Avastin, Genentech) and a dexamethasone intravitreal implant, said Mark C. Gillies, MBBS, PhD.[1]

The results were from a 12-month analysis of the 2-year BEVORDEX study, a phase 2, prospective, multicenter, randomized, single-masked clinical trial that included 88 eyes at 4 Australian sites and compared the efficacy of the dexamethasone intravitreal implant (n = 46) to bevacizumab (n = 42) for treatment of DME. Bevacizumab was administered every 4 to 6 weeks; the dexamethasone implant was administered every 4 to 6 months. Both treatments were administered as-needed.

A gain of 10 or more letters, the study's primary endpoint, was seen in 40% of eyes treated with bevacizumab compared with 39% of eyes in the implant group ($P = .83$). In the bevacizumab group, no eyes lost 10 letters or more, while in the implant group, 11% of eyes lost 10 letters or more, but unoperated cataracts may explain some of the visual acuity loss in the implant group, according to the researchers. The mean improvement in visual acuity was 8.9 letters for the bevacizumab group and 5.6 letters for the dexamethasone implant group ($P = 24$).

Mean CMT was 380.6 µm in the bevacizumab group and 285.0 µm for the dexamethasone implant group ($P = .007$). Patients in the bevacizumab group received a mean 8.8 injections; patients in the dexamethasone implant group received a mean 2.8 injections.

"We found no significant difference between the 2 groups with respect to vision gain," Dr. Gillies reported, adding that the dexamethasone implant "generally achieved better anatomical outcomes with substantially fewer injections."

1. Gillies MC, Lim LL, Campain A, et al. BEVORDEX--A multicenter randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for persistent diabetic macular oedema. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

BRAMD: No Difference Between Bevacizumab and Ranibizumab

No significant difference in visual acuity was found in patients with wet AMD who were treated with bevacizumab or ranibizumab in the BRAMD trial, a double masked clinical trial conducted in the Netherlands, reported Ann-Sofie M. Schauwvlieghe, MD.[1]

Patients were randomized to receive either 0.5 mg ranibizumab or 1.25 mg bevacizumab for 12 months. The mean gain in BCVA, the primary endpoint, was 5.1 letters (±14.1 letters) in the bevacizumab group and 6.4 letters (±12.2 letters) in the ranibizumab group ($P = .37$). In the bevacizumab group, 24% of patients gained 15 letters or more, 11% lost 15 letters or more, and 65% gained or lost fewer than 15 letters. In the ranibizumab group, 19% of patients showed a gain of 15 letters or more, 5% showed a loss of 15 letters or more, and 76% showed a gain or loss of fewer than 15 letters. No differences in absolute central retinal thickness and central retinal thickness change at 12 months were observed ($P = .13$) and the bevacizumab group showed more sub- or intraretinal fluid on optical coherence tomography than the ranibizumab group (45% vs 31%, $P = .020$).

1. Schauwvlieghe Am, Dijkman G, Hooyman JM, et al. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. BRAMD. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

IVAN: Lesion Size, Activity Associated With Vision Outcomes

Active and large lesions in wet AMD patients were associated with reading fewer ETDRS letters at baseline in the IVAN trial, and the number of ETDRS letters read at baseline predicted whether 68 letters or more would be read at the final visit, according to Geeta Manon, MBBS.[1]

According to Dr. Manon, patients with more active lesions read 9.4 fewer letters ($P < .0001$) at baseline, as did patients with larger lesions (1.6 letters per quartile, $P = .03$). ETDRS letters read at baseline and 3 months independently predicted reading 68 letters or more at the final visit ($P < .0001$). Larger lesion area (but not activity) and being classified in the worst quartile of ETDRS letters at baseline predicted longer time to lesion reactivation ($P < .002$); median time to lesion reactivation was 78 days. None of the factors investigated predicted the need for 3 injections or fewer per year.

1. Menon G, Yang TC, Gibson MJ, et al. Predictors of visual acuity outcome and time to lesion reactivation when using anti-VEGF drugs to treat wet AMD. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

RAP Lesions, No Subretinal Fluid, Ranibizumab Use Associated With Fewer Injections in CATT

Retinal angiomatous proliferation (RAP) lesions, no presence of subretinal fluid, and use of ranibizumab were associated with fewer anti-VEGF injections for AMD treatment in CATT, reported Daniel F. Martin, MD.[1]

Included in the analysis were 501 participants who had at least 20 of 26 possible opportunities for treatment. Patients with RAP lesion had 10.6 injections; patients without RAP lesions had 13.7 injections ($P = .001$). Patients with no subretinal fluid had 11.7 injections compared with 13.9 injection in patients with extrafoveal fluid and 13.4 injections in those with foveal fluid ($P = .04$). Patients who had no subretinal pigment epithelium fluid had 11.5 injections; patients with fluid not in the foveal center had 13.9 injections and those with fluid in the foveal center had 15.6 injections ($P < .001$).

1. Martin DF, Ying G, Huang J, Maguire MG. Predictors of the number of injections among patients treated PRN with ranibizumab or bevacizumab in the Comparisons of AMD Treatments Trials (CATT). Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Baseline Age, Visual Acuity Indicated Suboptimal Response in VIEW1 and VIEW2

Age, visual acuity at baseline, lesion size at baseline, and lesion size change from baseline to endpoint were indicators for suboptimal response to ranibizumab or aflibercept in the VIEW1 and VIEW2 trials, reported Paolo Lanzetta, MD.[1] Response variables included change in visual acuity and fluid status at weeks 52 and 96; descriptive variables included demographic and disease characteristics at baseline and during treatment, according to Dr. Lanzetta.

When suboptimal response was defined as a loss of 3 lines or more from baseline at week 52 or week 96, baseline lesion size, lesion size change from baseline to week 52, age (all $P < .001$), and visual acuity at baseline ($P < .05$) were associated with losing 3 lines or more at week 52. When suboptimal response was defined as a loss of 3 lines or more from baseline to week 96, associated variables included baseline lesion size and lesion size change from baseline to week 96, as well as age and visual acuity at baseline (all $P < .001$).

1. Lanzetta P, Cruess AF, Janosi I, et al. Characteristics associated with suboptimal response in patients treated with anti-VEGF therapy for wet age-related macular degeneration (wAMD). Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

No Association Between Aspirin, Progression of AMD in AREDS2 Data Analysis

There was no association between aspirin use and the progression of AMD or development of neovascularization or geographic atrophy (GA) among patients in AREDS2, said Mary E. Aronow, MD.[1]

According to a review of subjects in AREDS2 with no neovascularization or GA at the time of enrollment, aspirin propensity score adjusted for age was not associated with AMD progression (odds ratio [OR] = 0.80; 95% CI; *P* = .5076). When outcomes were analyzed individually, neither GA (OR = 1.31, 95% CI, *P* = .5688) nor neovascularization (OR = 0.60, 95% CI, *P* = .3049) were associated with the aspirin propensity score.

"Contrary to previous reports of association of aspirin use with advanced AMD, especially neovascular AMD, observational data from … AREDS 2 suggest that the use of aspirin has no statistically significant association with AMD progression," Dr. Aronow reported.

1. Aronow ME, Klein ML, Clemons TE, et al. Effect of aspirin use on progression of age-related macular degeneration in the Age-Related Eye Disease Study 2 (AREDS2) participants. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.

Postmarketing Survey: Less Frequent Adverse Events with Ocriplasmin Than in Clinical Trials

The rates of some adverse events associated with the use of ocriplasmin (Jetrea, ThromboGenics) appear to be lower in clinical practice compared to experiences in a phase 3 clinical trial, reported Marc D. de Smet, MDCCM, PhD.[1]

Rates of vitreous floaters, photopsia, retinal tear/detachment, and lens subluxation were all significantly lower among 6903 patients followed since the release of the drug compared to rates among 465 eyes studied during the clinical trial. Dr. de Smet said that the low number of reported postmarketing floaters could be due to doctors explaining to patients that vitreous floaters are part of the release process.

In the clinical trial, there were 56 (12.0%) reported cases of photopsia compared with 53 (0.8%) in the postmarketing surveillance. Retinal tear/detachment occurred in 3 (0.6%) eyes in the clinical trial compared with 19 (.03%) in the real world. There was 1 case of lens subluxation in the postmarketing group (0.01%). ■

1. De Smet MD. Postmarketing data of ocriplasmin injections. Symposium presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-8, 2014; Orlando, FL.