

In the News: A Retinal Update

Recapping the newsworthy events of 2012, as originally featured in *Retina Today*.

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The field of retina has witnessed numerous significant developments in the past year. Several drugs for the treatment of a range of retinal diseases gained US Food and Drug Administration (FDA) approval, and multiple milestone clinical trials were conducted. Additionally, major advances were seen in innovative treatments for retinal degenerative diseases, including retinal prostheses and stem cell therapy. This article recaps some of the major newsworthy events of 2012 that are likely to affect patients, their treatment, and the physicians who deliver their care.

JANUARY 2012

Stem Cell Therapy Was Safe, Improved Vision in Patients With Macular Degeneration

Researchers reported that subretinal transplantation of human embryonic stem cell (hESC)-derived retinal pigment epithelium (RPE) cells showed no adverse safety issues and yielded slight visual improvements in two patients with macular degeneration. The RPE cells were developed by Advanced Cell Technology (ACT).

The study¹ included the first two patients, one with dry age-related macular degeneration (AMD) and one with Stargardt macular dystrophy, in ACT's prospective phase 1/2 clinical trials to receive stem cell therapy. Four months after treatment, no hyperproliferation, tumorigenicity, ectopic tissue formation, apparent rejection, or adverse safety signals were detected. Both patients showed some visual improvement, and neither lost vision.

1. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *The Lancet*. 2011;379(9817):713-720.

FEBRUARY 2012

Second Study of Integrin Peptide Therapy Initiated

Allegro Ophthalmics LLC began its second human study using integrin peptide therapy for the treatment of vascular eye diseases such as wet AMD and diabetic macular edema (DME). Integrin peptide therapy is a small, anti-integrin oligopeptide that shuts off vascular endothelial growth factor (VEGF) production by blocking activation of VEGF receptors, inhibiting

tyrosine kinase, and causing a posterior vitreous detachment and vitreous liquefaction to increase VEGF turnover.

Because the molecule binds to multiple integrin-receptor sites and blocks multiple angiogenic pathways, it may be more potent and longer lasting than current anti-VEGF treatments. The second human study will include 30 patients with DME. Patients are receiving three monthly injections as a loading dose, with a total of 180 days follow-up.

CABERNET Brachytherapy for AMD Study Did Not Meet Primary Endpoint at 2 Years

The CABERNET study evaluating epimacular brachytherapy (NeoVista) for the treatment of wet AMD did not achieve its primary visual acuity endpoint at 2 years. The multicenter, prospective, randomized study included 457 treatment-naïve patients. Patients in the treatment arm underwent strontium-90 beta radiation with epimacular brachytherapy and two mandatory ranibizumab (Lucentis; Genentech) injections. Patients in the control arm received ranibizumab injections only, following a protocol that included three initial monthly injections followed by injections at least once every 3 months; rescue therapy was permitted. The primary endpoint was the percentage of patients losing fewer than 15 letters of vision. In patients treated with epimacular brachytherapy, six injections were required at the 2-year mark for a mean 2.5 letter loss, whereas patients treated with ranibizumab required 11 injections and achieved a mean 4.4 letter gain.

MAY 2012

CATT, IVAN Showed Equivalence of Ranibizumab and Bevacizumab for Wet AMD

Two-year results from the prospective Comparison of Age-Related Macular Degeneration Treatment Trials (CATT), comparing bevacizumab (Avastin; Genentech) and ranibizumab, showed that the drugs were equivalent in treating wet AMD when administered using similar dosing regimens.¹ A total of 1,185 patients with wet AMD were randomized to receive ranibizumab monthly, ranibizumab as needed, bevacizumab monthly, or bevacizumab as needed. At 1 year, patients

assigned to monthly treatment were randomly assigned to continue monthly treatment or switch to as-needed treatment, and patients initially assigned to as-needed treatment continued that regimen. Among patients following the same regimen for 2 years, the mean gain in visual acuity was similar for patients assigned to either drug. The mean gain was greater with monthly treatment than with as-needed treatment. At 2 years, the mean increase in letters of visual acuity from baseline was 8.8 in the ranibizumab monthly group, 7.8 in the bevacizumab monthly group, 6.7 in the ranibizumab as-needed group, and 5.0 in the bevacizumab as-needed group.

Evidence of the drugs' similar effectiveness was also seen in the 1-year results of the Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) study in the United Kingdom. This multicenter trial included 610 patients who had untreated wet AMD and could read 25 letters or more on the Early Treatment Diabetic Retinopathy Study chart. Patients were randomized into four groups: ranibizumab or bevacizumab, administered monthly or as needed with monthly review. At 1 year, the comparison between bevacizumab and ranibizumab was inconclusive, and discontinuous treatment was found to be equivalent to continuous treatment.

1. Presentation of One-Year IVAN and Two-Year CATT Study Results. Paper presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; May 6, 2012; Fort Lauderdale, Florida.

QLT091001 Improved Vision in Patients With RP, LCA

Treatment with QLT Inc.'s oral synthetic cis-retinoid (QLT091001) yielded visual improvements in patients with retinitis pigmentosa (RP) or Leber congenital amaurosis (LCA) due to either of two genetic mutations.^{1,2} One international, multicenter, open-label phase 1b study included 17 patients with early-onset RP due to mutations in the genes expressing RPE protein 65 (RPE65) or lecithin:retinol acyltransferase (LRAT). Participants received a dose of QLT091001 once daily for 7 days with follow-up at 7, 14, and 30 days. After treatment, average Goldmann visual field area improved from baseline by 22% at day 7, 16% at day 14, and 18% at day 30. The average retinal areas showed statistically significant improvements as well, and 65% of patients achieved an improvement in BCVA in at least one eye of 5 letters or greater. QLT091001 also showed an acceptable safety profile.

A second study was performed in patients with LCA due to mutations in the RPE65 or LRAT genes. In the study, 14 patients underwent 7-day therapy with QLT091001. Eight patients maintained longer-term improvements in Goldmann visual field, BCVA, or both after 7 days of treatment. Several patients reported improvement in daily-life activities, and no serious adverse events were seen.

1. Cideciyan AV, Moore AT, Zrenner E, et al. Increased vision within days of oral cis-retinoid (QLT091001) treatment in blindness due to mutations in retinal pigment epithelium-specific protein 65kDa (RPE65) or lecithin retinol acyltransferase (LRAT). Paper presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; May 10, 2011; Fort Lauderdale, Florida.
2. Koenekekoop RK, Esteban E, Wood L, et al. Update on QLT091001 in subjects with Leber congenital amaurosis due to lecithin retinol acyltransferase (LRAT) or retinal pigment epithelium protein 65kDa (RPE65) mutations. Paper presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; May 9, 2011; Fort Lauderdale, Florida.

Patient Regained Useful Sight After Receiving Retina Microchip

The first patient in Asia to be implanted with Retina Implant AG's microchip reportedly regained useful sight after being legally blind for 15 years due to RP. Following implantation, the patient in China was able to see both light and dark and, in a laboratory setting, was able to read letters projected on a screen, the company reported.

JUNE 2012

Anti-PDGF/Anti-VEGF Combination More Effective Than Ranibizumab Alone for Wet AMD

In a phase 2b study, the platelet derived growth factor (PDGF) inhibitor E10030 (Fovista; Ophthotech Corp.), in combination with ranibizumab, showed statistically significant superior efficacy over ranibizumab alone for the treatment of wet AMD.¹ Patients (n=449) were randomized to receive one of the following treatment regimens administered every 4 weeks for 24 weeks: 0.3 mg E10030 plus 0.5 mg ranibizumab, 1.5 mg E10030 plus 0.5 mg ranibizumab, or sham plus 0.5 mg ranibizumab. At 24 weeks, patients who received the combination of 1.5 mg E10030 and ranibizumab gained a mean of 10.6 letters, compared with 6.5 letters for patients who received ranibizumab monotherapy, representing a 62% additional benefit. Enhanced visual outcomes of anti-PDGF combination therapy as compared with ranibizumab monotherapy were shown at every monthly time point.

1. Ophthotech's Novel Anti-PDGF Agent Fovista Demonstrated Superior Efficacy over Lucentis Monotherapy in Large Controlled Wet AMD Trial [news release]. <http://www.ophthotech.com/news/>. Accessed October 20, 2012.

JULY 2012

ACT Began Treatment in Second Patient Cohort

ACT initiated treatment in a second patient cohort of its US clinical trial for Stargardt macular dystrophy using RPE cells derived from hESCs. In July, the first patient in the second cohort (fourth patient in the study) underwent surgery at Wills Eye Institute in Philadelphia. The patient was injected with 100,000 hESC-derived RPE cells in an uneventful, successful transplantation surgery. ACT is also conducting a clinical trial in patients with dry AMD and a second trial in Stargardt macular dystrophy in the United Kingdom.

AUGUST 2012

Alimera Sciences to Resubmit Application to FDA

Although the FDA stated it was unable to approve the new drug application (NDA) for Iluvien in November 2011, pSivida Corp., announced in August that its licensee Alimera Sciences intended to resubmit its application for Iluvien for DME. The company anticipated that the resubmission would focus on the population of patients with chronic DME, the indication for which several European countries have approved Iluvien.

Earlier, Alimera reported that it received a positive response from its decentralized procedure application to market Iluvien in Europe as a treatment for DME. It has since gained marketing authorization in Austria, Portugal, the United Kingdom, France, and Germany.

FDA Approved Ranibizumab for DME

The FDA approved ranibizumab for the treatment of DME, based on Genentech's RISE and RIDE studies. In these studies, patients with DME who received 0.3 mg ranibizumab experienced significant, early (day 7), and sustained (24 months) improvements in vision. Improvements observed at 24 months were maintained with continued treatment through 36 months.

Cause of Photoreceptor Death in RP Identified

Researchers at the Massachusetts Eye and Ear Infirmary identified the mode of death of cone photoreceptor cells in an animal model of RP.¹ Investigating whether receptor interacting protein (RIP) kinase-mediated necrosis was involved in the death of photoreceptor cells, the researchers found that RIP kinase is involved in cone degeneration and that a deficiency of RIP kinase reduced cone loss. It was also determined that treatment with a drug that inhibits RIP kinase significantly delayed cone cell death and preserved cone photoreceptors.

1. Murakami Y, Matsumoto H, Roh M, et al. Receptor interacting protein kinase mediates necrotic cone but not rod cell death in a mouse model of inherited degeneration. *Proc Natl Acad Sci USA*. 2012;109(36):14598-14603.

SEPTEMBER 2012

FDA Approved Eylea for Macular Edema following CRVO

The FDA approved aflibercept (Eylea; Regeneron) for the treatment of macular edema following central retinal vein occlusion (CRVO) based on data from the phase 3 COPERNICUS and GALILEO studies. In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters of BCVA at 24 weeks. Primary endpoint results for the aflibercept 2-mg monthly group were superior to those for the sham-treated control group.

INTREPID Study Met 1-Year Efficacy Endpoint

The INTREPID study, evaluating the efficacy and safety of one-time radiation therapy (IRay; Oraya Therapeutics, Inc.) in conjunction with as-needed anti-VEGF injections for the treatment of wet AMD, met its primary endpoint.¹ The IRay is a stereotactic radiotherapy system that delivers low-voltage x-rays through the sclera to a single treatment spot on the macula. The sham-controlled, double-masked trial included 230 patients with wet AMD who had received at least three anti-VEGF injections in the previous year and required ongoing anti-VEGF treatment. Within 2 weeks after injection, one-third of patients received a sham exposure and one-third each

received a radiation dose of either 16 or 24 Gy. Patients were followed monthly and treated with ranibizumab as needed. The trial achieved its primary endpoint, demonstrating a statistically significant reduction in as-needed anti-VEGF injections after 1 year. The treated patients required approximately 35% fewer injections than the sham group, with similar or improved visual acuity outcomes. No radiation-related adverse events occurred at the 1-year endpoint. The IRay device has received Conformité Européenne (CE)-Mark approval.

1. Jackson TL. INTREPID data and its significance. Paper presented at: the 12th Euretina Congress; September 8, 2012; Milan, Italy.

LUMINOUS Trial Data Showed No New Safety Signals for Ranibizumab

No new safety signals were observed in a large trial of ranibizumab for the treatment of wet AMD.¹ The ongoing observational LUMINOUS study consists of two parts that were launched in 2011. The retrospective phase comprises pooled data from four European registries of nearly 4,500 patients with wet AMD treated with ranibizumab. These data showed no new safety signals for ranibizumab and revealed a low incidence of key adverse events at 12 months. In patients who completed the first year of the study, the mean number of ranibizumab injections administered was low (range, 4.7–5.5). After 12 months of treatment, patients had an average visual acuity gain of 7 letters, and the incidence of treatment-related adverse events was less than 1%. The study currently has more than 5,500 enrolled participants and is expected to recruit more than 30,000 patients from clinics in Asia, Australia, Europe, North America, and South America. The final study results are expected to be published in 2016.

1. New data for Novartis drug Lucentis confirms long-term efficacy and safety profile and benefits of individualized treatment [news release]. Basel, Switzerland: Novartis; September 5, 2012. <http://www.novartis.com/newsroom/media-releases/en/2012/1638671.shtml>. Accessed October 15, 2012.

OCTOBER 2012

FDA Panel Recommended Approval of the Argus II

The FDA Ophthalmic Devices Advisory Panel recommended approval of the Argus II Retinal Prosthesis System (Second Sight Medical Products Inc.), voting 19-0 that the system's probable benefit outweighs its risks, according to the manufacturer. The panel, which is composed of experts in ophthalmology, retinal disease, low vision, electrophysiology, and other specialties, heard testimony from the FDA and several doctors and participants involved in the company's most recent clinical trial conducted in patients with end-stage RP. Second Sight submitted its application for approval of the Argus II in May 2011 based on the results of this trial, which began in 2007 and followed a successful clinical trial of the earlier Argus I.

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The Argus II received CE-Mark approval in March 2011. The system works by converting video images, captured by a miniature camera housed in the patient's glasses, into a series of small electric pulses that are transmitted wirelessly to an array of electrodes on the retinal surface. These pulses are intended to stimulate the retina's remaining cells, resulting in corresponding perceptions of patterns of light in the brain. Patients can learn to interpret these visual patterns, thereby gaining some functional vision.

Neural Stem Cells Implanted in Patient With Dry AMD

StemCells, Inc., announced that the first patient in its phase 1/2 clinical trial in dry AMD has been enrolled and treated with its proprietary purified human neural stem cells (HuCNS-SC) product candidate. The study will enroll 16 patients and is designed to evaluate the safety and preliminary efficacy of HuCNS-SC cells as a treatment for dry AMD. Preclinical data published earlier this year¹ demonstrated that HuCNS-SC cells protected host photoreceptors and preserved vision in an animal model, and that the number of cone photoreceptors remained constant over an extended period.

1. McGill TJ, Cottam B, Lu B, et al. Transplantation of human central nervous system stem cells – neuroprotection in retinal degeneration. *Eur J Neurosci.* 2012;35(3):468-477.

FDA Approved Ocriplasmin for Symptomatic VMA

The FDA approved ocriplasmin (Jetrea; ThromboGenics NV) for the treatment of symptomatic vitreomacular adhesion (VMA). Ocriplasmin is the first pharmacologic agent to be approved for this indication, according to the manufacturer. The approval was based on data from the company's phase 3 MIVI-TRUST program.¹ The program consisted of two multicenter, randomized, double-masked trials that included 652 eyes, comparing a single intravitreal injection of ocriplasmin (125 µg) with placebo in patients with symptomatic VMA. The investigators found that VMA resolved in 26.5% of ocriplasmin-treated eyes and in 10.1% of placebo-injected eyes. Treatment with ocriplasmin was associated with some ocular adverse events, which were mainly transient. ThromboGenics reported that it is continuing to prepare for the planned launch of ocriplasmin in January 2013 through its own US commercial organization. Market surveys conducted by the company estimate that approximately 500,000 patients annually in the United States and the major markets of the European Union could potentially benefit from ocriplasmin. ■

1. Stalmans P, Benz MS, Gandorfer A, et al; for the MIVI-TRUST Study Group. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. *N Engl J Med.* 2012;367:606-615.