A Glance at Retina Presentations at ARVO 2015

Judging by the topics covered, there is no shortage of new therapies in development.

BY ARON SHAPIRO AND ORA STAFF MEMBERS

The theme of this year's Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Denver, Colo., was "Powerful Connections," and, as always, the meeting provided an opportunity for clinicians, scientists, and industry specialists to convene and talk about everything in ophthalmology. This installment of the Innovations column reviews some of the new developments in retina that were presented, discussed, dissected, and digested at ARVO 2015. (Presentations are referenced parenthetically in an abbreviated format in the text below: first author: e-abstract number.)

NEW METHODS OF DELIVERING THERAPY

In recent years, significant research efforts have been dedicated to improving the treatment options and visual outcomes of patients with age-related macular degeneration (AMD). The introduction of VEGF inhibitors offered a means of preventing permanent vision loss, and even improving vision. However, the necessity of monthly or bimonthly intravitreal injections still remains. Presentations at ARVO 2015 highlighted several novel delivery systems in development to address this limitation.

DeCogan et al presented a de novo–designed system of cell-penetrating peptide constructs fused to a therapeutic protein transduction domain (DeCogan F: 4147). In vivo, the system successfully transported microgram quantities of macromolecules, such as the large monoclonal VEGF inhibitors, in a topically administered drop that penetrated to the back of the eye.

Other presentations focused on slow-release depots of VEGF inhibitors. Initial in vitro pharmacokinetic work was presented on controlled-release polymer reservoirs of ranibizumab (Lucentis, Genentech; Abe T: 4146). Extended release of the drug from the polymeric system was demonstrated over 150 days, during which ranibizumab also retained its activity. A noninvasive electroosmotic method for delivery of bevacizumab (Avastin, Genentech) was reported to be comparable to the efficacy of intravitreal bevacizumab in a rabbit model of choroidal neovascularization (CNV; Molokhia S: 2293). Compared with the control group, the electroosmosis-bevacizumab treatment suppressed neovascularization for an average of 4 weeks, while the intravitreally injected bevacizumab suppressed neovascularization for 8 weeks.

Kong et al described a novel polymer nanoparticle system for delivery of anti-VEGF therapies (Kong L: 5029). Bevacizumab conjugated to the biodegradable vehicle reduced leakage of the drug into the bloodstream. This resulted in prolonged retention time in the vitreous, potentially making it safer and more effective by both reducing systemic exposure and extending ocular residence time.

Several presentations examined in vitro and in vivo properties of extended-release bevacizumab-packaged microparticles. These included pharmacokinetic studies of solid state microparticles within sustained-release hydrogel matrices in both primate and nonprimate species (Tully S: 222; Owens G: 236; Verhoeven RS: 230). It is likely that future ARVO presentations will focus on the refinement of these delivery approaches.

Presentations on steroid therapy for retinopathy also had a presence this year. A dexamethasone intravitreal implant (Ozurdex, Allergan), together with macular grid laser, was found to be effective for patients with macular edema secondary to branch retinal vein occlusion (BRVO; Massaro D: 3752). The combination improved visual acuity and allowed increased time between injections. Using a proprietary technology, biodegradable dexamethasone-polymer implants and microparticle suspensions were created for sustained, slow release of drug for intravitreal delivery (Das S: 4165). Sustained-release kinetics of loteprednol (Lotemax,

Bausch + Lomb) in a nanoparticle gel for the treatment of CNV were also presented (Hirani A: 5038). Topical dexamethasone gamma-cyclodextrin nanoparticle eye drops decreased macular thickness in patients with diabetic macular edema (Ohira A: 2289). Study participants also showed improvement in visual acuity.

Investigations of novel small-molecule therapies continue. Initial in vitro screens of multiple new drug candidates were presented, including small molecule vitamin D receptor agonists (Merrigan S: 158); combinations of inhibitors of the P13K/Akt/mTOR pathway (Sasore T: 2305); and an isoquinolone sulfonamide derivative that inhibits protein kinase function (Sugimoto M: 150).

Previous research conducted at Trinity College Dublin established the efficacy of interleukin-18 (IL-18), a proinflammatory cytokine, in regulating CNV formation in mice.[1] In a presentation this year, these researchers determined that IL-18 immunotherapy was safe and efficacious in preventing laser-induced CNV in a nonhuman primate eye (Campbell M: 4803). The ocular and systemic pharmacokinetics of a topical receptor tyrosine kinase inhibitor formulated via a mucus-penetrating particle eye drop were assessed (Schopf L: 2279). After topical administration in several animal models, enhanced penetration and activity in the back of the eye were observed.

Studies of topical regorafenib (Stivarga, Bayer), a multikinase inhibitor, in rodents (Klar J: 246) and nonhuman primates (Beottger MK: 2294) were presented. Both presentations highlighted the efficacy of regorafenib drops and the possible benefits of a noninvasive, potentially self-administered formulation.

In other preclinical news, SH-11037, a homoisoflavanone synthetic derivative of cremastranone, significantly suppressed angiogenesis in a laser-induced CNV murine model when injected intravitreally (Sulaiman RS: 2470). Oral dosing of a chemokine receptor 3 (CCR3) antagonist effectively suppressed neovascularization in mice and primates (Ng Q: 2290). An oral docosahexaenoic acid derivative, ONO-A, inhibited neovascularization and had a protective effect on retinal damage in rat models of AMD (Ogami S: 2350). In a mouse model of oxygen-induced retinopathy, NK0144, a new RNAi-based agent, appeared to inhibit neovascularization promoted by the protein periostin (Nakama T: 2280).

Other work compared the anti–platelet-derived growth factor aptamer Fovista (Ophthotech) and the anti-VEGF agent aflibercept (Eylea, Regeneron) as monotherapy and combination therapy in a mouse model of retinal angiogenesis; benefits favored the combination (Walsh B: 2298). Lee et al demonstrated that GV1001, a telomerase-derived peptide, inhibited laser-induced neovascularization in a rat model (Lee EK: 2291).

CLINICAL TRIAL RESULTS

The ongoing BAM114341 study is investigating GSK933776, a therapy designed to block formation of beta-amyloid deposits, in patients with geographic atrophy secondary to AMD (Shearn SP: 2840). Presented at this meeting were results of a 4-month run-in period, in which fundus photography and autofluorescence images were used to define patient-specific growth rates of lesions before treatment. The monthly measurements taken during the observation period were consistent with estimated growth rates published in the literature. The efficacy results of this study will be much anticipated, given recent research linking beta-amyloid formation in AMD with other neurodegenerative disorders of peptide misfolding, including Alzheimer disease.

The 1-year results of a phase 1/2 study of combination low-dose proton beam irradiation plus anti-VEGF therapy were presented (Osmanovic S: 4806). The study was initiated based on the observed synergism of VEGF inhibition with radiation therapy in oncology. Interim analysis demonstrated that fewer injections were needed in the radiation group, with no safety concerns exhibited. Fewer injections for patients is meaningful, as it may indicate an overall reduction in treatment burden.

The final results of a phase 2 trial of 0.2% squalamine lactate topical therapy (OHR-102, Ohr Pharmaceutical) in combination with intravitreal ranibizumab for treatment of AMD were presented (Slakter JS: 4805). Marked improvements in visual acuity gain were seen with combination therapy in comparison with ranibizumab monotherapy; however, no decrease in injection frequency was observed.

Results with RTH258, a humanized single-chain antibody fragment, for the treatment of wet AMD were also presented (Berger B: 821). High responder rates were seen in both intravitreal injection and infusion cohorts, suggesting promise. Because this molecule has the potential advantage of microvolume injections or infusions, simultaneous treatments with additional therapies or sustained delivery becomes a viable option.

Positive results were announced for the phase 3 VIBRANT study, employing intravitreal injection of aflibercept for treatment of macular edema secondary to BRVO (Boyer DS: 3749). Using the proportion of patients with a 15-letter or greater gain in BCVA as primary endpoint, intravitreal aflibercept was superior to grid laser at 24 weeks and at 52 weeks.

Another trial compared bevacizumab with an intravitreal dexamethasone implant for treatment of diabetic macular edema (Gillies MC: 3144). Improvement of 10 or more letters at 24 months was similar in both groups

(bevacizumab 45%, dexamethasone 43%), but more subjects in the dexamethasone group showed a decline of 10 or more letters in BCVA (5/46 vs 1/42), and a significantly greater percentage of subjects in the dexamethasone group showed cataract progression.

GENE THERAPY

Gene therapy for inherited retinal diseases is showing great promise, and work in this field was prominent at this year's meeting.

Results were positive from a phase 1 study of a subretinally injected lentiviral vector (RetinoStat, Oxford BioMedica) in patients with wet AMD (Chandler S: 2284). This was a first-in-man application of a subretinally injected lentviral vector, in which a recombinant equine infectious anemia virus vector was used to deliver genes encoding the antiangiogenic proteins endostatin and angiostatin. This gene therapy approach was safe and well-tolerated, and patients showed signs of clinical benefit.

Researchers at Johns Hopkins School of Medicine presented research on the gene-editing CRISPR technology to develop genetically modified–induced pluripotent stem cells in an effort to generate 3-D retina reporter cell lines for the study of photoreceptors (Wahlin KJ: 3596).

Several presentations offered novel approaches to target oxidative stress. Biswal and colleagues demonstrated that delivery of genes for antioxidant enzymes can be used as a tool to reverse oxidative stress in a mouse model of retinal pigment epithelium oxidative stress (Biswal MR: 3189). Another presentation suggested that targeting specific transcription factors that regulate hundreds of genes that combat oxidative stress may be more effective than delivery of antioxidant enzymes (Xiong W: 3188).

AND MORE

As always with ARVO, the 2015 meeting featured too many fascinating poster sessions, presentations, and thoughtful discussion sessions to cover in a single article. The material outlined above barely scratches the surface of all that went on during the meeting. Still, we hope this review provided useful news of developments in retina research. See you in Seattle at ARVO 2016! ■

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1. Doyle SL, Ozaki E, Brennan K, et al. IL-18 attenuates experimental choroidal neovascularization as a potential therapy for wet age-related macular degeneration. *Sci Transl Med*. 2014;6(230):230-244.