

# News in Review

COMMENTARY AND PERSPECTIVE

## Promising Gene Tx Results at 2 Years

**A SMALL PHASE 1 CLINICAL TRIAL** has added greater confidence in the quest to treat 2 rare inherited retinal degenerative diseases caused by *RPE65* mutations: Leber congenital amaurosis (LCA) and severe early-childhood-onset retinal degeneration.<sup>1</sup> Not only was the gene therapy found generally safe but it also yielded improvements in visual acuity (VA) or other visual functions in 9 of 12 patients.

In the trial, 8 adults and 4 children—aged 6 to 39 years—underwent vitrectomy and received a subretinal injection of an adeno-associated virus vector expressing normal *RPE65* into retinal cells of the poorer-seeing eye at 1 of 2 doses. Patients were followed for 2 years, and the effectiveness of the treatment was evaluated by means of best-corrected VA (BCVA), visual field (VF), electroretinography, and quality-of-life questionnaires.

**Safety and effectiveness.** Patients experienced no serious adverse events related to treatment. Common adverse events associated with the surgical procedure included subconjunctival hemorrhage in 8 patients and ocular hyperemia in 5 patients.

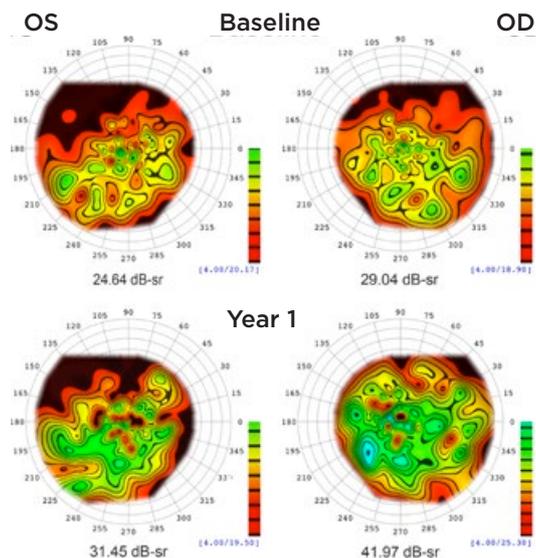
“The trial included several children, who had better baseline visual acuity and experienced better visual results than the adults,” said David J. Wilson, MD, study coauthor and director of the Oregon Health & Science University School of Medicine in Portland. This

was significant, he said, given that most safety trials generally look at patients with advanced disease.

At the 2-year visit, the 4 pediatric patients, whose baseline BCVAs were between 40 and 62 ETDRS letters, showed 6- to 14-letter increases in the treated eye. However, only 1 adult, who had a baseline BCVA between 20 and 31 ETDRS letters, experienced a 2.5-letter increase, while adults with baseline VA limited to counting fingers or hand movements showed no change in BCVA.

Apart from the VA improvements in 5 patients, other types of visual function improvements were reported in 9 of the 12 patients. These included increase in VF, loss of central scotoma, and subjective gain in vision in low light conditions.

**Novel analytic tool.** A unique feature of the trial was use of a novel VF analytic tool, called Visual Field Modeling and Analysis, developed by senior author Richard A. Weleber, MD. Compatible with a variety of VF devices, it allows accurate evaluation of both central and side vision, said Dr. Wilson. “Most visual field testing assesses the central visual field. But with many of these diseases, what is changing—and worth preserving—is the peripheral visual field. Having a tool that allows us



**VISUAL FIELD MODELING AND ANALYSIS.** Model represents VF changes seen in 1 trial subject from baseline to year 1. The right eye (OD) received gene therapy. Topographic iso-sensitivity lines have been drawn at 2-dB intervals. The calibration scale depicts the color coding for the iso-sensitivity lines, and the number just below the scale is the maximum sensitivity for the eye. The total volume in decibel-steradians (dB-sr) of the hill of vision ( $V_{tot}$ ) is indicated below each model.  $V_{tot}$  increased from 29.04 to 41.97 dB-sr in the OD and was accompanied by a marked decrease in nystagmus and improvement in fixation instability.  $V_{tot}$  increase in the OS is thought to be associated with the improvements in nystagmus and fixation.

to analyze that as an endpoint is very valuable.”

**Implications for the future.** Pre-clinical data suggest that retinal gene therapy has long-term effects, said Dr. Wilson, and the good responses seen in the children in this trial bode well for preventing progression of photoreceptor degeneration. Study participants will be followed for at least 15 years to more fully reveal the effects of therapy.

By proving safety, this trial helps advance the field, he said, and may speed FDA approval processes and make it

easier to develop similar viral vectors for other single-gene diseases.

Over the next 10 to 15 years, there will likely be substantial changes in gene therapy, said Dr. Wilson, including refinements in both delivery techniques and vector technology. "Most important, researchers developing these therapies need to stay very objective," he said. "Patients with these diseases are highly motivated, so we can't rely on their subjective feedback about what the treatment accomplishes."

—Annie Stuart

1 Weleber RG et al. *Ophthalmology*. 2016;123(7):1606-1620.

Relevant financial disclosures—Dr. Wilson: None.

## ANTIBIOTIC RESISTANCE

### Careful Rx May Limit the Problem

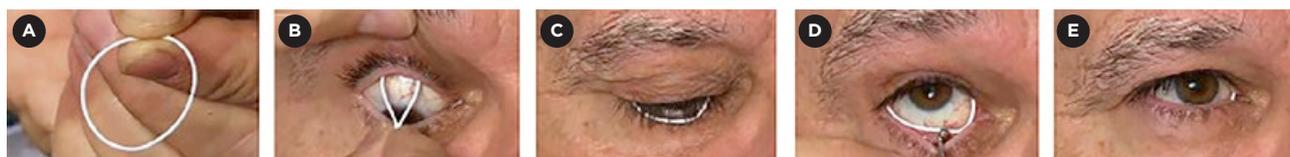
**ANTIBIOTIC RESISTANCE TO COMMON** ocular pathogens continues to be a challenge, according to the most recent data from the ongoing Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) Surveillance Study, presented at the 2016 Association for Research in Vision and Ophthalmology (ARVO) annual meeting.<sup>1</sup>

**New data, continuing trends.** The updated data are based on 441 isolates collected from 19 sites in 2015. The current findings follow a trend that has

been observed since 2009, when the nationwide multicenter survey began looking at resistance of common ocular pathogens to several commonly used antibiotics. The data show high levels of antibiotic resistance among staphylococcal isolates, especially among methicillin-resistant (MR) strains, with many isolates demonstrating multidrug resistance.

"This trend is here to stay; and even if it does not increase, the level is so high that not dealing with antibiotic resistance is not an option," said Penny A. Asbell, MD, MBA, professor, Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York.

**Key findings.** The report analyzed



## GLAUCOMA DRUG DELIVERY

### New 6-Month Insert vs. Drops

Physician encouragement doesn't go very far toward convincing many glaucoma patients to use their prescribed hypotensive medications, laments glaucoma specialist James D. Brandt, MD.

"Patients will come in and say, 'Oh, yeah, I'm still taking that drop every night.' Then you look at their pharmacy data in the EMR, and it's really quite shocking. You see that they haven't refilled their medication in 6 months," Dr. Brandt said.

**Countering noncompliance.** A topical insert intended to ameliorate this problem by bathing the ocular surface in bimatoprost continuously for up to 6 months is expected to begin a phase 3 efficacy trial later this year, said Dr. Brandt. Results of the phase 2 trial were recently published.<sup>1</sup>

The preservative-free ocular ring is 1 mm thick and 24 to 29 mm in diameter. It incorporates 13 mg of bimatoprost into a silicone matrix, with a polypropylene core for support. The ring is inserted into the conjunctival fornices, where the drug diffuses passively into the tear film.

**Phase 2 results.** Dr. Brandt, who is a professor of ophthalmology and visual science at the University of California, Davis, was the principal investigator in the phase 2 study. Using subjects who had open-angle glaucoma (OAG) or ocular hypertension (OHT), the masked trial compared outcomes over 6 months between 64 patients treated with the medicated insert

and sham drops (artificial tears) and 66 controls treated with 0.5% timolol drops plus a sham insert.

The researchers reported that intraocular pressure (IOP) fell by 3.2 to 6.4 mm Hg (about 20%) with the bimatoprost ring, compared with 4.2 to 6.4 mm Hg in the timolol group. The study size was too small to determine noninferiority compared with the timolol, but that will be tested in phase 3, according to the researchers.

**Clinical implications.** "In the Ocular Hypertension Treatment Study, we demonstrated that lowering IOP by just 20% among ocular hypertensives reduced the rate of conversion to OAG itself," Dr. Brandt said. "The bimatoprost insert is targeted at the millions of patients treated for OHT or early OAG who simply won't, don't, or can't take their medications."

But the real potential for this approach to hypotensive therapy lies beyond monotherapy, Dr. Brandt added. "To me, the biggest advantage is the versatility of this technological platform," he said. "The device has so much volume that I could easily conceive of having 2 or even 3 medicines in the ring." —Linda Roach

1 Brandt JD et al. *Ophthalmology*. Published online May 5, 2016.

Relevant financial disclosures—Dr. Brandt: ForSight VISION5; S,C; Glaukos: C,O.

organisms frequently implicated in bacterial eye infections; common ocular isolates submitted by labs nationwide include *Staphylococcus aureus* (SA), coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. The isolates were tested for susceptibility to as many as 15 antibiotics.

Following are some of the key findings:

- Resistance among staphylococci was most notable for azithromycin (54%-59%), oxacillin/methicillin (24%-45%), and ciprofloxacin (22%-28%).
- CoNS isolates exhibited substantial levels of resistance to trimethoprim (26%) and tobramycin (19%).
- 39% of CoNS isolates and 20% of SA isolates were resistant to 3 or more drug classes.
- Multidrug resistance remained prevalent among MRSA (67%) and MRCoNS isolates (74%).
- Resistance among *P. aeruginosa* isolates continues to be low, and *H. influenzae* isolates were generally susceptible to all antibiotics tested.

**Advice for clinicians.** “Choosing the best antibiotic to use is not trivial,” said Dr. Asbell. It requires determining the possible organism and its sensitivities and the antibiotic’s ability to penetrate the target tissue, as well as its biocompatibility or safety profile, she said.

Dr. Asbell advised clinicians to keep handy the tables from the 5-year ARMOR surveillance study, including more than 3,200 isolates, published last year in *JAMA Ophthalmology*.<sup>2</sup> “The ARMOR data can be useful for selecting your first antibiotic to use, especially if fortified compounded antibiotics are not available,” she said. “These data should be used hand-in-hand with local antibiograms from hospitals to aid therapy selection and improve antibiotic stewardship.”

Dr. Asbell offered further recommendations for prescribing antibiotics:

- Don’t prolong treatment.
- Don’t use antibiotics to treat allergies and/or viral infections.
- Consider antibiotic cycling/rotation based on resistance trend data.
- Emphasize the importance of treat-

ment adherence to your patients.

ARMOR is continuing to collect ocular isolates from centers nationwide. In the meantime, Dr. Asbell urged clinicians to “choose the antibiotic wisely” for the initial treatment, since not all antibiotics will work on all isolates. Then check culture results to adjust as the clinical course demands. “Clinical assessment still counts,” she said. “Each case needs to be considered individually.”

—Miriam Karmel

1 Sanfilippo CM et al. Antibiotic Resistance Profiles of Ocular Pathogens—An Update from the 2015 ARMOR Surveillance Study. Poster presented at: ARVO Annual Meeting; May 4, 2016; Seattle.

2 Asbell PA et al. *JAMA Ophthalmol.* 2015;133(12):1445-1454.

**Relevant financial disclosures**—Dr. Asbell: Bausch + Lomb: C (unrelated to this article).

## LOW VISION AIDS

# Novel Device Improves Daily Functioning

**RESEARCHERS AT UNIVERSITY OF California, Davis, Eye Center** report that legally blind patients were able to read newspapers, books, and menus, and recognize products and signs with the help of an artificial vision device that is as portable as a pair of spectacles.<sup>1</sup>

The system, called OrCam, consists of a miniature camera and a bone conduction earpiece that are mount-

ed to the side of almost any spectacle frame and connected by a thin wire to a pocket-sized battery and computer. By pointing a finger or pushing a button, the wearer indicates the text or item of interest, which the device reads to the patient through the earpiece. It can be programmed to recognize faces, products, and paper money.

Developed in Israel, the device is available in the United States and Canada. Currently, it works only in English.

**Tested on daily tasks.** In this pilot study, the 12 participants were asked to perform tasks from a list of 10 items that simulate daily visual activities. These included reading emails on electronic devices, newspaper headlines or articles, menus, or signs, as well as identifying money or products. At baseline, the mean task score (1 point per task completed) was 2.5 with patients’ best-corrected vision (20/200 or worse in the better-seeing eye). With the OrCam device, all participants could perform at least 9 of 10 such tasks (mean score, 9.5).

**Not like a magnifier or app.** “The OrCam is a unique low vision aid that is not a magnifier and is different from smartphone applications or voice-activated devices,” said Elad Moisseiev, MD, a retina fellow at UC Davis.

“If anything, the optical character recognition technology driving OrCam is closer in spirit to a self-driving motor vehicle. It helps users recognize text, objects, and faces, but not by making them more visible,” explained Mark J. Mannis, MD, the ophthalmology department chair at UC Davis. “The users do not actually ‘see’ with it but are able to recognize text and objects of interest that are in front of them, improving their functionality and independence.”

—Miriam Karmel

1 Moisseiev E, Mannis MJ. *JAMA Ophthalmol.* Published online May 5, 2016.

**Relevant financial disclosures**—Drs. Mannis and Moisseiev: None. The OrCam company provided devices for use during the study.



**ORCAM IN USE.** Patient points to text of interest, and the device reads it into the earpiece.

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at [www.aao.org/eyenet](http://www.aao.org/eyenet).