GENE THERAPY

Novel Treatment Improves Vision in Teen

A NEW TYPE OF GENE THERAPY approved under the FDA compassionate use program has improved vision in the right eye of a teenage boy with a severe ocular form of dystrophic epidermolysis bullosa.

Missing proteins. Antonio Vento, 15, was born with the rare genetic condition, which affects about 3.3 million people around the world. He told his doctors at Bascom Palmer Eye Institute, in Miami, that prior to the treatment, “it was like looking through thick fog. I had trouble distinguishing the smaller numbers and letters in my [video] games.”

Dystrophic epidermolysis bullosa is caused by mutations in an inherited gene, \( \text{COL7A1} \), which codes for a protein that makes type VII collagen. This type of collagen helps give skin its structure. People with dystrophic epidermolysis bullosa have very fragile skin and mucous membranes that blister and tear easily, which leads to extensive scarring. Ocular manifestations linked to the condition are common, but traditional treatment options are not very effective.

An alternative to surgery. Antonio’s longtime ophthalmologist, Alfonso Sabater, MD, PhD, Associate Professor of Clinical Ophthalmology at Bascom Palmer Eye Institute, said two previous surgical treatments were performed by one of his partners in 2016 and 2017. But when Antonio’s vision deteriorated again due to scar tissue buildup, he wanted to explore other avenues.

“After each eye surgery, the scar tissue came back in the same places, but even worse than before,” said Dr. Sabater, who is also Medical Director of Bascom Palmer’s Ocular Surface Program and Director of the Corneal Innovation Lab.

B-VEC treatment. At an office visit about three years ago, Dr. Sabater learned that Antonio was enrolled in a dermatology clinical trial investigating a novel topical gene therapy, beremapavec (B-VEC), to promote wound healing and skin integrity. This therapy utilizes a replication-defective herpes-simplex type 1 viral vector to transflect normal \( \text{COL7A1} \) genes into epithelial cells, restoring their ability to express \( \text{COL7} \) type II collagen protein. Dr. Sabater noted the positive dermatology trial outcomes and approached the drug’s manufacturer, Krystal Biotech, to reformulate B-VEC as an ophthalmic solution that could possibly slow or even reverse Antonio’s vision loss.

The FDA granted compassionate use approval for Antonio after two years of efficacy and safety testing. And in August 2022, Dr. Sabater operated on Antonio’s right eye to remove scar tissue obstructing his cornea followed by application of the specially formulated eye drops (a total of 19 cumulative doses).

In a case study published in the New England Journal of Medicine, Dr. Sabater and colleagues reported that routine dosing of the ophthalmic B-VEC eye drops in the right eye following symblepharon lysis surgery significantly reduced cicatization in Antonio’s right eye. Full healing of the corneal epithelium was observed three months after the surgery and regular use of topical B-VEC.

“Eight months after surgery, slit-lamp biomicroscopic examination showed complete epithelial healing, and images obtained by optical coherence tomography (OCT) showed no evidence of corneal scarring or infiltrates,” they wrote.

Antonio’s visual acuity in the right eye, classified as “hand motion” before
the surgery and treatment, was 20/25 within the first eight months of treatment, and the case study authors said the eye showed no lingering evidence of corneal dysfunction or symblepharon recurrence.

Future vision. Emily McCourt, MD, Chief of Pediatric Ophthalmology at Children’s Hospital Colorado Anschutz Medical Campus, in Aurora, said the recent case study gives her hope.

“From the perspective of a pediatric ophthalmologist, dystrophic epidermolysis bullosa is a difficult-to-treat, painful, and potentially blinding condition,” she said. “I am extremely excited about the potential use of gene therapy to treat patients with [the condition] and am hopeful this opens the door to more options for treating other difficult ocular surface diseases.”

According to Dr. Sabater, his young patient still experiences visual limitations, but the success of this treatment has had a huge impact on Antonio’s life.

“He’s reading, he’s homeschooling, and he’s playing video games with his friends again,” said Dr. Sabater.

In May 2023, the FDA approved B-VEC for the treatment of dystrophic epidermolysis bullosa wounds on the body. But the federal agency has not yet approved the topical treatment for the eye. But the success of this treatment has had a huge impact on Antonio’s life.

“Unfortuately, some of those things trend together, and in the paper, we demonstrate the distribution of SVI scores. Those really indicate how a geographic variable is associated with worse initial disease.”

It is important to recognize the impact of social determinants of health, including barriers to accessing eye care and variations in insurance coverage, said Sally Liu Baxter, MD, MSc, Assistant Professor and Division Chief for Ophthalmology Informatics and Data Science at the Shiley Eye Institute at the University of California, in San Diego.

Study significance. Dr. Baxter said that the findings build upon prior studies that show a link between socioeconomic disparities and worse cases of OAG, and the study’s size adds weight to previous findings.

“The dataset used in this study has nationwide scope and includes data from multiple practice settings, as opposed to being limited to academic medical centers. However, its generalizability may still be limited given that the majority of practicing ophthalmolo-
gists in the United States do not use the Epic electronic health record system,” said Dr. Baxter, who was not involved with the study.

**Catching disease early.** “One of the main challenges of glaucoma is that it can be a symptomless disease in the early and moderate stages. Patients often don’t experience any pain, and often they don’t see any discernible changes in their vision. This means that they can have glaucoma but remain undiagnosed until the disease is advanced,” Dr. Baxter said.

Even with symptoms, some people can face greater barriers to accessing eye care—and medical care in general —and as a result, the initial diagnosis can be delayed, leading to more severe disease at onset, she said.

**From findings to solutions.** Dr. Swaminathan said research like this can help target who is in most need of screenings and interventions, adding that it is less about targeting a predominantly Black or Hispanic neighborhood and more about using the study findings, which offer a geographic marker that indicates areas with greater vulnerability, to come up with a plan.

With these findings, he said, “Screening activities could be set up in certain areas to reach high-risk individuals, so that they do not wait a long period of time to receive care.”

Dr. Baxter said that clinicians could also do a better job of encouraging patients with glaucoma to educate their families and communities and encourage their networks to see a clinician for an evaluation.

**Insurance.** “Another consideration from a clinical and health policy perspective is that many patients may have insurance but are effectively underinsured if they struggle to find physicians who will accept their insurance. We see this with Medicaid patients, where some physicians will not accept patients on Medicaid, or their health systems and upper management will not allow them to see patients on Medicaid,” Dr. Baxter said. “This presents another barrier to care for patients.”

**Raising awareness.** Dr. Swaminathan hopes clinicians will develop more awareness of which individuals are at greater risk for severe disease.

“Clinicians may need to spend more time counseling and discussing medication, and visit adherence with patients who are high-risk to minimize poor outcomes,” he said.

The study findings are “just a piece of the puzzle,” he said, adding that he hopes to continue researching how factors associated with social determinants meaningfully affect patient outcomes.

—Brian Mastroianni

**SEEING PAST SPECKLES.** NEI scientists combined AI with AO-OCT to explore a more efficient method of visualizing the RPE cell mosaic in healthy human eyes.

1 Swaminathan SS, Medeiros FA. Am J Ophthalmol. 2024;263:50-60.

**AI-BASED IMAGING**

**Exploring a New Approach to Retinal Imaging**

**RESEARCHERS AT THE NATIONAL**

Eye Institute (NEI) have developed an artificial intelligence (AI) method that—when combined with adaptive optics optical coherence tomography (AO-OCT)—improved their ability to visualize retinal pigment epithelial (RPE) cells in images taken from participants with healthy eyes.

Their study, published in *Communications Medicine*, describes how integration of AI with AO-OCT helped minimize “speckle noise,” a phenomenon that obscures details in images of the RPE. Their experimental AI-driven imaging technique provided results faster than current retinal imaging methods, the authors wrote.

**Overcoming speckle noise.** When ophthalmologists want to take a close look at the retina and the RPE, AO-OCT allows the visualization of RPE cells by capturing high-resolution 3D images of the retina. But due to speckle noise, which obscures cellular details in the average AO-OCT image, hundreds of 3D images are typically required to improve contrast and visualization of the RPE.

“We wanted to contribute a more efficient way to image the RPE cells directly in the living human eye,” said author Johnny Tam, PhD, who leads NEI’s Clinical and Translational Imaging Section, in Bethesda, Maryland.

Dr. Tam and colleagues developed a novel deep learning algorithm they call P-GAN, or parallel discriminator generative adversarial network. By “feeding” it close to 6,000 manually analyzed AO-OCT images of human RPE, they trained the network to identify and recover features of RPE images that are not obscured by speckles—in other words, teaching it to work around the speckles to reconstruct the cellular tissue hidden behind them.

“We leveraged natural eye motion to reconstruct a large number of images for each location, increasing the size of our training data by over 40-fold,” said Dr. Tam.

**Speeding up the RPE imaging process.** Application of the AI method to eight eyes in seven healthy participants showed that using the P-GAN method improved RPE cell contrast by 3.5-fold.
compared to the traditional AO-OCT method. And it reduced the time required for RPE visualization by nearly 100-fold compared to traditional averaging methods, the authors reported.

Using P-GAN, the researchers could capture the RPE mosaic across large retinal areas (63 overlapping locations) in a much shorter time frame than the six hours it takes with traditional methods, Dr. Tam said.

According to the authors, RPE cell spacing in AI-recovered images agreed with expected normative ranges from previous studies.

More validation needed. “The results are impressive with improvement over previous optical or AI-based methods,” said retina specialist Tien Y. Wong, MMed (MD), PhD, MPH, MBBS, Founding Head of Tsinghua Medicine at Tsinghua University in Beijing, China, and Consulting Professor in the Department of Ophthalmology at Duke University, in Durham, North Carolina.

However, fidelity remains a concern with P-GAN networks, cautioned Dr. Wong, who was not involved in the study.

Dr. Tam said if validated, AI implementation could enhance routine ophthalmic imaging and allow earlier detection of retinal diseases affecting RPE cells.

“Adaptive optics can reveal cellular details, but the imaging window for each acquisition is small, and the patient needs to remain still for a long time to stitch together a larger image,” said Dr. Tam. But a dramatic improvement in speed, like that demonstrated in their study, “would allow us to better link cellular-scale findings to tissue-scale clinical imaging by capturing a population of cells and following them over time.”

Research involving participants with eye diseases. Future studies would also need to evaluate the performance of P-GAN in diseased eyes, where RPE cell appearance and contrast may differ from healthy eyes, said Dr. Tam. His team plans to expand the potential of AI-assisted imaging by exploring its application to other retinal cells and structures, such as ganglion cells and blood vessels.

“This is an exciting time for ophthalmology because of this amazing intersection between imaging and AI,” said Dr. Tam. He is hopeful that the incorporation of AI into imaging will eventually help lower the barrier to deploying adaptive optics by making it easier to obtain high-quality images.

Reflecting on the broader implications of integrating AI with imaging modalities, Dr. Wong said, “Combining advanced imaging methods with AI is the future for optical imaging devices.”

—Christos Evangelou, PhD

Relevant financial disclosures—Dr. Tam: None.
Dr. Wong: None.

See the financial disclosure key, page 12. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.