Inherited Retinal Disorder: In Vivo CRISPR Therapy Provides Vision Improvements

Inherited retinal disorders (IRDs) are the leading cause of visual impairment, affecting approximately 1 in 2,000 people of all ages worldwide (1). There are many types of IRDs, each caused by a gene variant that affects how the retina functions, with one of the most severe being Leber Congenital Amaurosis (LCA). The early-onset condition is the leading cause of inherited blindness in children and occurs in about three out of 100,000 newborns.

LCA is often caused by a mutation in the *CEP290* gene. Among mutations known to cause *CEP290*-IRD, the single A>G nucleotide change within intron 26 is the most common and is present in up to 77% of cases in the United States (1). The nucleotide change introduces a cryptic exon in *CEP290* messenger RNA that leads to a premature stop codon and termination of protein synthesis in half of the *CEP290* transcripts. Full-length expression of *CEP290* is disrupted, leading to insufficient protein levels to form the photoreceptor segments (1).

The resulting disease is characterized by disorganized rod and cone photoreceptors in the eye, with disorganized outer segments and early death of photoreceptors in the mid-peripheral retina. This eventually leads to irreversible vision loss, akin to a small section of an engine breaking down, eventually causing the entire thing to falter. Currently, there is no available treatment for *CEP290*-IRD, and the standard of care focuses on supportive interventions, including glasses, magnifiers, high-contrast reading materials, canes, home modifications, and braille (1).

However, cones in the macula (the central part of the retina) are retained, and the optic nerves and occipital cortices may also remain structurally intact, presenting an opportunity to

intervene and target the spared photoreceptors to restore vision, which is what a recent clinical trial aimed to do (2).

BRILLIANCE trial - a landmark in the treatment of retinal genetic conditions

CRISPR-Cas9 is a gene editing tool that acts like a pair of molecular scissors, cutting DNA at a specific location so bits of DNA can either be added or removed. In the BRILLIANCE study, the drug EDIT-101, which contains CRISPR gene-editing components, was injected under the retina of the eye so it could cut out the mutation in *CEP290* and restore the gene's ability to produce the protein responsible for light-sensing cells.

The study assessed the safety and efficacy of a single escalating dose of EDIT-101 in 14 patients with *CEP290*-IRD, a cause of Leber congenital amaurosis (LCA). The trial started in 2019 with 12 adults ages 17 to 63 and two children ages 9 and 14. The children are the first congenitally blind children to be treated with gene editing, which significantly improved their daytime vision.

"Our hope is that the study will pave the road for treatments of younger children with similar conditions and further improvements in vision," Tomas S. Aleman, MD, and study co-author, explained in a recent article, adding that the trial represents a landmark in the treatment of genetic diseases, and specifically blindness, by offering an important alternative treatment.

Among the adult volunteers, two received a low medication dose, five were given an intermediate dose, and five received a high dose, while both the children received the intermediate dose (1).

Since the study's primary outcome was safety, each participant had the EDIT-101 drug injected into only one eye. The secondary analysis focused on efficacy, which was measured through the change from baseline in visual acuity, a full-field test that assessed how well participants saw colored points of light while looking into a specialized device, how well they could navigate a research maze with physical objects and varying amounts of light, and quality of life.

After the procedure, the patients were monitored every three months for a year, with less frequent follow-ups continuing for two additional years (1).

BRILLIANCE study results show improved quality of life

College student Olivia Cook, who had only a small degree of central vision, was one of the 14 participants in the trial. Before receiving the treatment in her left eye, it was as if she was seeing the world through a straw hole. In dimly lit places, she could only make out silhouettes and was unable to see people's faces.

Around nine months after the surgery, Cook had an "aha moment" when she noticed something in her peripheral vision she'd never been able to before: a candle flickering. Noticing Christmas lights wrapped around a balcony railing and her friends' faces glowing in the twinkling lights during dusk was another new experience for her. Her untreated right eye is still unable to make out facial features and can only see silhouettes.

The clinical results mirror Cook's positive experience, finding that six participants improved from the baseline in the vision-related quality of life score (1). Six participants also showed a meaningful improvement from baseline in cone-mediated vision, and five of these six also showed improvement in at least one other key outcome (1). Nine participants had a meaningful improvement in either their baseline in the best corrected visual acuity, sensitivity to red light, or the score on the mobility test (1). Additionally, all participants but three had improvement in at least one of four key efficacy outcomes, and six had improvements in two or more outcomes. Four participants had a clinically meaningful improvement in the best corrected visual acuity, and nearly half had a visually meaningful improvement in cone photoreceptor function, of whom all but one had an improvement in at least one other outcome. The six participants with a visually meaningful improvement in the study, which included both children, received either an intermediate or high dose of EDIT-101. Of these six, three adult participants received the high dose, while one adult and both children received an intermediate dose.

The meaningful improvements in the participants' vision started at three months and continued through subsequent visits (1). The study concludes that its results support the safety of EDIT-101 to the extent that safety can be assessed in a small study and notes that follow-up over an extended period will be needed to evaluate long-term risks associated with off-target effects of gene editing. Additionally, the study states that the vision improvements support further research of in vivo CRISPR-Cas9 gene-editing to treat IRDs like *CEP290*-IRD (1).

While the results are positive, complete vision has not been restored among the participants. Most participants couldn't read an eye chart before the study, and only four of them have had some improvements in this ability. However, some patients have said that following treatment, they can now see their cell phones light up, differentiate the different foods on their plates, or even notice vibrant sunsets.

Michael Kalberer, 46, received the drug in his right eye and started to notice improvements in his vision about two to six months later. The treatment allowed him to experience the colorful strobe lights on the dance floor of his cousin's wedding, which before the surgery would have only been shadows. While Kalberer described the treatment as groundbreaking, he noted his disease is not cured, but the progression has slowed.

The results, however, are a valuable reminder of the importance of quality of life for patients, explained Art Caplan, a professor of bioethics and founding head of the Division of Medical Ethics at NYU Grossman School of Medicine's Department of Population Health, in a recent article. "Usually, when we're doing gene therapies or other innovative interventions, we associate them with saving lives. This experiment is a huge reminder that quality of life matters. This is about vision," Caplan said. "No one's dying. No one's saved. But restoration of vision is an important achievement, and it's a reminder that quality of life has to be factored into what we decide to cover in terms of insurance reimbursement and what we try to study."

Being able to find a misplaced phone or know the coffee machine is working by seeing its small lights may seem trivial to those with normal vision, but it can have a high impact on the quality of life for those without it, Mark Pennesi, MD, PhD, study co-author noted.

No adverse events or signs of harm caused by EDIT-101

There were no serious adverse events related to the treatment or procedure, and the adverse events that did occur were mild or moderate. These events included one patient experiencing some eye-bleeding following the surgery, and, once cleared, their vision returned to baseline. Two adult participants who received the high dose of EDIT-101 had subretinal hyperreflective mounds on OCT imaging, a symptom the researchers say has been seen in other studies involving subretinal gene therapies and is thought to be inflammation, though the cause is unclear. One did not experience any vision changes, and the mounds resolved without treatment. The other experienced vision impairment related to the mounds, but the patient's vision improved after a course of steroids.

There were also no signs that the CRISPR gene-editing caused ripple-effect harm to the patients' genomes. Though the editing is designed to be permanent, it is not expected to be passed down to the offspring of those who receive it due to its localized effect. No viral genomes were detected in semen, although viral genomes were detected in tears, nasal mucosa, and blood of some participants for a short time after treatment.

"The primary goal of this first-in-human study was to test the safety of using CRISPR-Cas9 gene editing *in vivo*. When we started the trials, the subjects who were treated were the first patients ever to have received CRISPR-Cas9 gene-editing treatments *in vivo*," Dr. Eric Pierce, the study's first author and the director of the Ocular Genomics Institute at Mass Eye and Ear and Harvard Medical School said in a recent article. "There were no serious adverse events related to the treatment or the surgery required to deliver the treatment and no dose-limiting toxicities."

The future of gene therapies in treating IRDs

Since genetic variants cause most IRDs, gene therapy is a compelling treatment option. Direct treatment into the eye allows more efficient delivery to the target tissues and reduces potential exposure to other body systems. Additionally, the eye's "immune privileged" status, which protects it from the immune system, means there's a lower likelihood that the gene therapy will be rejected via an immune system attack. Gene therapy is only given once, unlike other retinal disease treatments that are needed more frequently.

Currently, Luxtrana is the only FDA-approved gene therapy for adults with an IRD. The drug is designed for patients with biallelic *RPE65* mutation-associated retinal dystrophy. A mutation in the *RPE65* gene, which provides instructions to make an enzyme needed for normal vision, leads to vision loss and sometimes complete blindness. While CRISPR gene therapy directly edits the gene, Luxtrana works by delivering a working *RPE65* gene directly to retinal cells through a naturally occurring adeno-associated virus. The retinal cells can then produce the normal protein needed to convert light to an electrical signal in the retina to restore vision loss.

As for the future of EDIT-101, Editas Medicine, which funded the study, paused further trials of CRISPR gene editing as a treatment for *CEP290*-IRD in November 2022 in view of the small population and has instead continued to follow up with the trial participants.

The team is working with Editas to find an additional commercial partner for Phase 3 studies and hopes the publication will stimulate biotech and pharmaceutical interest. Further research could provide insights into the long-term effects of treating patients with the CRISPR-Cas9 gene editing tools, which will remain in their bodies for the rest of their lives.

"I think the real risk that we're all concerned about with CRISPR-Cas9 gene editing is: Could the gene editing machinery that we've introduced into the retinal cells of these patients do something else, somewhere else in the genome, in addition to the therapeutic activities that it was designed for?" Pierce said. "Could a cut in the genome be made ten years from now that could have an adverse effect over time? I think the answer to that is yes, it could. But we're hopeful that risk is very low. That's what we need additional follow-up for."

The researchers hope future studies can examine ideal dosing, whether a treatment is more effective in certain age groups, and include refined endpoints to measure how improved cone functioning impacts activities of daily living.

For the trial participants, who can now see the food on their plates or the faces of their loved ones, the drug has given them a treatment that did not previously exist. Olivia Cook, whose vision in the treated eye is not completely restored but can see things she has never seen before, said her life has mostly changed in that she's more hopeful that there will be more scientific findings in the future.

References:

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