Sustained safety, efficacy of gene therapy for inherited retinal disease

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Three years ago, preliminary but encouraging results were announced regarding the safety and success of gene therapy in a small cohort of patients with an inherited form of blindness known as Leber congenital amaurosis (LCA). Now, researchers at the Perelman School of Medicine at the University of Pennsylvania and the Scheie Eye Institute, have taken the next major step in their pursuit of treatment for this previously incurable vision loss by showing continued safety and efficacy of gene therapy in a larger and age-diverse group of LCA patients.

"We now have evidence of safety and efficacy of this novel treatment in five groups of patients over a wide age range and with persistence of efficacy for at least three years," said Samuel Jacobson, MD, PhD, professor of Ophthalmology, and principal investigator of the clinical trial. "We had an original single injection strategy that has been advanced to two injections in the same eye in children and adults. The goal to increase the extent of functioning vision has been achieved, all the while maintaining a safety-first approach."

The new research, published online this week in the *Archives of Ophthalmology*, documents in detail the progress of 15 patients, ages 11 - 30 years, who all received an injection of genes into the retina of one eye for the type of LCA caused by a mutation in the RPE65 gene. This gene normally makes a critical protein in the visual cycle. Without this RPE65 protein, light-sensitive photoreceptor cells are starved of a retina-specific form of vitamin A and cannot function, blocking vision. The gene therapy entails taking a normal copy of the mutated gene and directly introducing it into the retinas of affected individuals.

The study tracked the continued progress of all patients treated and found that visual function improved in everyone to different degrees. The improvements were predictably localized to treated areas.

"Counterintuitive was the finding that some of the greater success stories of this treatment were in the 'older' patients," added Dr. Jacobson. "We previously found no simple relationship between age and amount of disease and now conclude that to focus only on very young patients for trials of this condition may be excluding some very appreciative candidates. High technology micro-scanning techniques are widely available and must be used to identify which areas of the eye are amenable to treatment. We identify and then treat areas with greater potential, independent of patient age."

The team of researchers from the Perelman School of Medicine included Samuel G. Jacobson, MD, PhD, professor of Ophthalmology, and Artur V. Cideciyan, PhD, research professor of Ophthalmology, both at Penn Medicine's Scheie Eye Institute, along with additional colleagues at Penn and William W. Hauswirth, PhD, professor of Ophthalmology, and his colleagues at the University of Florida, Gainesville.

"This work greatly extends our knowledge of gene therapy for patients with LCA," said Joan O'Brien, MD, professor and chair of the Department of Ophthalmology at the Perelman School of Medicine, and director of the Scheie Eye Institute. "The success of therapy in patients at older ages increases the population who will benefit from this vision restoring work. Through the techniques elucidated in this paper, more functionally blind patients will receive useful vision."

In addition to the safety and efficacy findings, the new research also proposes strategies for next steps to advance this new treatment to clinical reality for this and other forms of LCA.

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