

Leber Congenital Amaurosis: Safety, Efficacy in Early Clinical Investigation

Three adult patients with LCA2 show signs of efficacy with no serious adverse effects.

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Leber congenital amaurosis (LCA) is a group of inherited diseases with onset of severe vision loss beginning in childhood and blindness usually ensuing by the third or fourth decade of life.¹ A number of variants are associated with different genetic mutations. One of these, LCA2, is associated with mutations in the RPE65 gene. That gene encodes a protein involved in the production in photoreceptors of a chromophore that is necessary for vision.^{2,3} Although the absence of this protein causes early profound visual impairment in humans and animal models, the degeneration of the retinal cells themselves is delayed. Unlike in degenerative retinal diseases, the cells remain present, though not functioning, even after blindness has set in and electrophysiologic response is nearly absent.^{2,4}

This pathophysiologic characteristic makes LCA2 a disease possibly suited for gene therapy. If, by insertion of the correct gene, the function of the retinal cells can be repaired before degeneration takes place, it should be possible to measure the effect of this application relatively quickly.

This approach has been shown to be effective in animal models. In a canine model of LCA2, an attenuated adeno-associated virus (AAV) vector containing RPE65 complementary DNA (cDNA), injected subretinally, resulted in rapid development of vision. Ongoing observation of these animals has now exceeded 8 years, and long-term restoration of visual function continues.⁵

Based on these results, we have investigated the safety and efficacy of this approach in humans, and we recently reported early results of a phase 1 trial in three adult patients with LCA2.⁶ This article reviews the results of that study and presents further reflections on the status of this trial and prospects for future investigation.

TRIAL DESIGN

A replication-deficient AAV vector containing RPE65 cDNA was injected subretinally in three consecutive patients with LCA2. The patients were between 19 and 26 years of age when enrolled in the trial. A standard three-port vitrectomy was performed, and the posterior cortical vitreous was removed to allow injection into the subretinal space of the vector and cDNA in a volume of 150 μ L of buffered saline. The injections created localized dome-shaped retinal detachments in the treated eyes of the patients.

Preoperatively and at intervals postoperatively, the patients underwent complete ophthalmic examination, physical exam, and tests including assessment of the biodistribution of the vector and immune response.

Efficacy was evaluated using both subjective and objective measures performed preoperatively and at least 1 month postoperatively. Objective measures included pupillary light reflex and nystagmus testing. Subjective measures included logMAR visual acuity, visual field, and mobility testing in a standardized obstacle course.

SAFETY AND EFFICACY RESULTS

In all three patients, the localized retinal detachments resolved within 14 hours after surgery. Postoperative examinations were unremarkable, except that one patient developed a macular hole that has not expanded since postoperative day 14. No serious adverse events were seen. No evidence of immune response to the application or systemic biodistribution of vector DNA sequences was seen in any patient.

At baseline, in all patients, pupillary light reflex to alternate stimulation of the left and right eyes showed much less sensitivity to light than in control subjects. Baseline responses to stimulation with 0.04 lux in dark-adapted

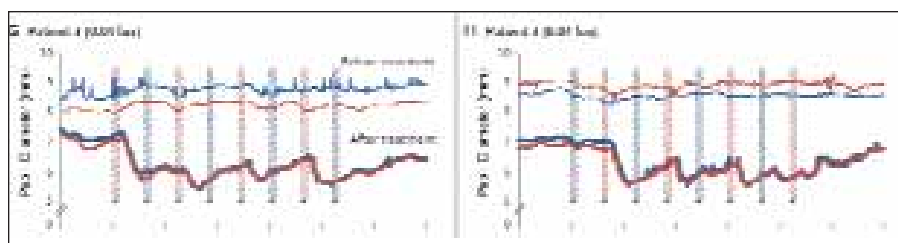


Figure. The pupillary light reflexes for Patient 3 at baseline and 1 month after injection are shown after alternating stimulation with 0.04 lux, first in the right eye and then in the left eye, respectively. (Reprinted with permission from Maguire et al.⁶)

patients were negligible, and responses to 10 lux (250 times brighter) were weak.

After injection, pupillary response in patients' treated eyes (in all cases the right eye) was greater than in the untreated eyes. This was so even though the treated eye in each case was the patient's worse eye. The eyes that received injections became approximately three times more sensitive to light than they had been at baseline and surpassed the sensitivity of the previously better untreated eye. The patients therefore demonstrated an apparent relative afferent pupillary defect, with the treated eye responding to the light stimulus and the untreated eye remaining defective (Figure).

At 2 weeks after surgery, all patients reported improved vision in mesopic conditions. All patients showed improvements in visual acuity logMAR scores from baseline, with increases equivalent to between three and 4.5 lines on the Snellen acuity chart. There was a trend toward improvement in visual field area in all three subjects. All patients demonstrated reduction in frequency and amplitude of nystagmus, both monocular and binocular.

DISCUSSION

In this phase 1 evaluation, treating the genetic disease LCA2 with subretinal injections using a gene-therapy delivery system appeared to be safe and showed signs of efficacy in terms of improvement in retinal and visual function. Although these are short-term results, we believe they are significant, as they represent the first demonstration of an effect from in vivo gene therapy in humans.

Considering the short-term nature of these phase 1 study data, we set a high standard for ourselves before publishing information on efficacy. We insisted on a minimum of three patients with a minimum of at least one subjective and one objective finding of efficacy. Visual field, visual acuity, and obstacle course testing all have subjective elements or the possibility of a placebo or learning effect. Pupillometry has no placebo or learning effect; it is a valid, objective measure of visual function. Also, pupillometry is a more sensitive measurement than

electroretinography, which can be problematic in patients such as these with severe lack of retinal function.

By demonstrating an afferent pupillary defect in the untreated eye with pupillometry, we have unequivocal evidence in three out of three patients that nicely supports our subjective findings of improvement in visual acuity.

LCA2 is one subset of a rare disease, but the proof of principle achieved in this study has implications for many other diseases. Our next step may be to look at similar therapy in patients with Stargardt's disease, but one should not get the impression that this gene therapeutic approach will work only in hereditary diseases. It has the potential to work in any disease in which a gene or segment of DNA or a DNA product can be shown to have a therapeutic effect. Other centers are currently investigating therapies for age-related macular degeneration using the same AAV vector used in our study.

Since the time of our report, we have treated three more patients with LCA2 with no safety issues interrupting the study to date. Data from these patients are still being analyzed. The original three patients in the study continue to do well.

We believe that results in LCA2 may be further improved by applying the gene treatment earlier in the course of the disease, before nystagmus and amblyopia have set in. This means, in other words, treating a pediatric population, so further evaluation of the safety of the procedure may be needed before that is undertaken. ■

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