

Gene therapy for vision restoration in patients with Leber congenital amaurosis (LCA) due to *RPE65* gene mutations: beginning the phase IV trial

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Abstract

This is a significant time in the field of gene therapy in humans. Recently, results from a phase III clinical trial were published, demonstrating the first gene therapy success for a genetic disease. A clinical trial was carried out in patients a hereditary blindness disease named Leber congenital amaurosis, which is caused by mutations in the RPE65 gene. Participating subjects received a subretinal injection of the normal RPE65 gene and one year after exhibited a significant improvement in visual acuity. It is expected that this gene therapy treatment will be approved by the FDA and commercialized in the USA in 2017.

KEY WORDS: Leber congenital amaurosis. LCA. RPE65. Retinal dystrophy. Gene therapy. Blindness. AAV. Phase III clinical trial.

Inherited retinal dystrophies (IRD) is a group of genetic diseases characterized by photoreceptor cells (rods and cones) progressive dysfunction and death, which results in progressive vision loss and blindness in those affected. To date, approximately 250 genes implied in different IRDs have been identified, which turns this group of disorders into one of the most common forms of hereditary disease in humans. IRDs are a model of disease where gene therapy has been used for treatment, and protocols are currently underway for conditions such as Leber congenital amaurosis (LCA), Stargardt disease, IB-type Usher Syndrome, pigmentary retinosis due to *MERTK* gene mutations and choroïderemia². LCA is the most serious and early form of IRD and it occurs in approximately 5% of IRD total cases. At least three clinical findings suggest the LCA diagnosis: a) serious visual impairment or blindness with onset prior to one year of age, b) absence of pupillary reflexes and c) highly diminished or undetectable

electroretinographic responses³. Absence of visual fixation and nystagmus can also be early observed, even since the 6th week of life. In these patients, there is high retinal phenotypic variability, which ranges from normal eye fundus or with mild retinal involvement, to maculopathy, pigmentation with “bone-spicule” morphology or coloboma⁴.

LCA is inherited in an autosomal recessive pattern and at least 22 genes are known to be associated with the disease. Proteins encoded by these genes participate in processes that are important for vision, such as visual cycle, phototransduction, retinal pigmentary epithelium phagocytosis and photoreceptor development, among others⁴.

LCA caused by mutations in *RPE65* is classified as LCA2 and accounts for 6%-16% of all cases of LCA⁴. Patients with LCA2 are characterized for exhibiting nyctalopia, nystagmus and impaired vision with onset before one year of age. These patients can experience an

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improvement in visual function during the first years of life and acceptable vision during adolescence, but between the third and fifth decades of life they experience progressive and permanent visual deterioration⁴. The development of LCA2 animal models with similar characteristics to their human counterparts and the use of adenovirus-associated viruses (AAV) that release *RPE65* cDNA in the retina have demonstrated sustained restoration of the visual function. Based on these preclinical studies, several clinical trials were initiated in 2007 for *RPE65* gene therapy in humans, and preliminary results began to be published in 2008⁵. This way, groups from the Pennsylvania Children's Hospital and the Pennsylvania and Florida Universities in the USA, as well as from the Moorfields Institute in England, have generated phase I/II clinical data^{5,6}. Although in all studies AAV were used as vectors, the comparison of results has been difficult due to differences in the gene therapy product (doses, promoters, potentiating sequences), injection administration site in the retina, patient selection criteria and timing of participants' assessment. In October 2015, the Spark Therapeutic company, associated with the Pennsylvania Children's Hospital, overtook other groups and has published phase III data on the treatment with their gene therapy product for LCA2, known as SPK-RPE65. The main variable of clinical improvement at this phase was a participants' mobility test using a maze, where patients had to follow black arrows on a white floor and step over and around obstacles until reaching the end in a room designed for this purpose. Patients were asked to complete the maze at seven different light levels (lux or illuminance units), from 1 lux (which is like the light on a moonless summer night) to 400 lux (equivalent to a brightly lit office)⁵, with the illuminance level required to adequately complete the maze being recorded. The study included 31 patients with LCA with confirmed mutations in the *RPE65* gene. All participants had severe visual impairment, although no one had complete blindness, and their ages ranged between 4 and 44 years. Of the 31 patients, 21 were included in the intervention group (subretinal injection of the SPK-RPE65 product), and the remaining 10 formed the control group that did not receive the injection. In the latter group, no patient had an improvement over the course of one year. In contrast, patients with LCA2 who underwent gene therapy showed notorious improvements with regard to the illuminance level at which they were able to successfully complete the

maze (difference of $p = 0.001$ in illuminance levels with regard to baseline level prior to the injection)⁶. Some of these patients had a drastic gain in comparison with baseline measurement⁵. In addition, three additional aspects were assessed in subjects who received the therapy and controls, with better results attained in treated subjects⁶. First, baseline retinal physiological function was assessed by measuring light sensitivity using a test known as full-field light sensitivity threshold testing (FST), where intervened subjects had a highly significant improvement of $-2.06 \log^{10}$, compared with a decline of $0.04 \log^{10}$ in controls ($p = 0.001$)⁶. In the second place, a study known as change in mobility test score was used to assess the mobility test through the maze after first eye injection (between baseline and one year post-treatment; $p = 0.001$)⁶. Last test measured central vision changes by assessing the subject's capability to read a standard eye chart (visual acuity). Intervened subjects showed an average improvement of approximately two lines (nine letters), as compared with 1.6 letters in the control group. Another important point to highlight in this study is that there were no adverse effects related to phase III with *RPE65* gene therapy⁶.

These results are the culmination of more than on decade of investigation and have a great significance for medical research, particularly in the area of the treatment of degenerative diseases of the retina. Patients with LCA2 who were treated with gene therapy, and who were otherwise destined to progress towards total blindness, showed significant vision restoration. Encouraged by these results, the Stark Therapeutics company has announced that it will request the registry of its product (Voretigene Neparvovec) to the FDA and will launch a marketing strategy for the initiation of phase IV trials of gene therapy for LCA2 in the USA from 2017 on.

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