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Editorial

Prospect of retinal gene therapy following commercialization of voretigene neparvovec-rzyl for retinal dystrophy mediated by RPE65 mutation

The approval of voretigene neparvovec-rzyl by the US Food and Drug Administration (FDA), in December 2017, marked the beginning of a new era in medicine in which many inherited diseases will be essentially corrected by gene therapy. Voretigene neparvovec-rzyl, with the trade name of Luxturna, is the first gene therapy for an inherited disease. It is intended for the treatment of RPE65 mutation-associated retinal dystrophy, making it the second commercially available treatment for inherited retinal disease (IRD) after retinal prostheses (Argus II and Alpha IMS) which were commercialized a few years earlier. Unlike retinal prostheses, voretigene neparvovec-rzyl modifies the course of the disease.

Voretigene neparvovec-rzyl is composed of human RPE65 cDNA along with a cytomegalovirus enhancer and a hybrid chicken β-actin promoter incorporated into a recombinant adeno-associated virus 2 (AAV2). Following injection into the subretinal space, AAV2 enters retinal pigment epithelial (RPE) cells. While the viral vector remains in episomal form in the nucleus, without integrating into the host DNA, the enhancer and promoter facilitate expression of RPE65.

Retinitis pigmentosa (RP) is the most common IRD, and Leber's congenital amaurosis (LCA) is a severe form of IRD presenting at birth or childhood. Affected patients present with nyctalopia and peripheral visual field defect followed by central vision loss in advanced stages of the disease. Currently, mutations in approximately 300 genes are known to cause IRD. Mutations in RPE65 account for approximately 2% of autosomal recessive RP and 16% of LCA.[1] Although an uncommon cause of IRD, several factors have made RPE65 a favorite target for gene therapy: 1) It causes autosomal recessive IRD, in which gene replacement is sufficient to treat the disease. 2) About two decades ago, when gene delivery methods were being developed, RPE65 was one of only over a dozen genes that were known to cause IRD. 3) The relatively small size of RPE65 gene makes it possible to be carried by AAV2. 4) The clinical course of LCA in which photoreceptor cell loss significantly lags behind the functional loss, provides a window in which retinal function may be restored in the residual cells. 5) The existence of a large animal model of LCA with RPE65 mutation made it possible to carry out gene therapy in dogs and paved the way for human clinical trials.

RPE65 mutations were first implicated in childhood IRD in 1997 by two independent groups of investigators.[2,3] In 2001, briard dogs with RPE65 mutation were successfully treated by gene therapy delivered through subretinal injection; the same study indicated that intravitreal delivery was not effective.[4] The positive results of a phase 1 human clinical trial in 2009 followed by a successful phase 3 trial in 2017 lead to the approval of voretigene neparvovec-rzyl.[5,6]

The future of gene therapy for IRD is promising; however, there are challenges ahead:

1) Gene therapy requires viable cells and hence will not be effective in advanced stages of IRD with severe photoreceptor degeneration. Optogenetics, in which ganglion cells are transformed into photosensitive cells via gene therapy, is an exception. However, since photoreceptors and outer retinal image processing are bypassed, the vision recovery in this approach may be limited. The results of an ongoing phase 1/2 clinical trial will provide first information regarding safety and efficacy of this method in human.
2) It is unclear whether gene therapy can prevent progression of retinal degeneration. Although human clinical trials on RPE65 gene therapy have demonstrated continued retinal degeneration despite functional improvement, studies on a canine model have indicated that early treatment in the dysfunction-only stage may be associated with preservation of remaining photoreceptors.[7,8] Future studies on patients implanted at an earlier stage will help to determine whether gene therapy can have a protective effect on photoreceptors and RPE.
3) Gene therapy is gene specific, and a new treatment for each gene has to go through all the steps of a drug development i.e. animal studies, clinical trials and

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regulatory processes. The huge cost involved in the process of drug development may leave little incentive for pharmaceutical companies to develop new treatments for the majority of IRD genes, which are less common and may not provide a sizable pool of patients who may benefit from the treatment. Optogenetics is an exception as it can be used for any outer retinal disease regardless of the cause. Unforeseen revolutionary discoveries or inventions might allow development of a common gene therapy method for different gene mutations, making it available to patients with uncommon or rare gene defects.

4) The ability of delivering genes to photoreceptors is limited by the cargo capacity of viral vectors. For example, USH2A, the most common mutated gene in autosomal recessive RP and a common gene defect in Usher syndrome, is too large to be carried by current vectors. Attempts are being made to address this problem by using multiple vectors for a single gene. In addition, future new vectors, or modifications to current vectors, may allow tackling this issue.
5) Mutations in genes such as RHO which cause autosomal dominant RP, are associated with dominant negative effects. Gene therapy for these conditions requires disruption of the mutated allele in addition to insertion of a functional copy of the gene. This problem may be overcome by the use of CRISPR-Cas9 [Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR-associated system 9 (Cas9)] system, which allows gene editing by introducing double-stranded breaks in DNA at precise locations. This concept is still in early stages but limited animal studies have had encouraging results.
6) The need for subretinal delivery of current vectors such as AAV2 and lentivirus for targeting photoreceptors and RPE cells necessitates vitrectomy and subretinal injection. This approach is associated with potential complications such as macular hole and retinal detachment, as well as long-term side effects such as cataract, which may have a bigger impact on pediatric patients. More importantly, only photoreceptors and RPE cells that are within the subretinal bleb are exposed to viral vectors. Vector modifications which may allow intravitreal delivery will be a major improvement, making gene therapy a safe, office based procedure, and allowing all photoreceptors and RPE cells to be exposed to the viral vector.
7) Although AAV2 is not pathogenic and has a favorable immunologic profile when delivered subretinally, a human clinical trial on age-related macular degeneration has suggested that pre-existent neutralizing anti-AAV2 serum antibodies may be associated with decreased efficacy of gene therapy when AAV2 is delivered intravitreally.[9] In addition, some patients showed increased or new anti-AAV2 serum antibodies following intravitreal injection. Further studies are warranted to verify these findings and evaluate their significance.

In summary, voretigene neparvovec-rzyl commercialization is a historic milestone in medicine and a turning point in our ability to modify the course of IRD. Future studies will demonstrate the long-term efficacy of this treatment and will guide us in developing new treatments for other mutated genes. Combination of economics and scientific discoveries will determine our success on this course.

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