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Current Perspective on Gene Therapies in Pediatric Ophthalmology

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Description

Genetic pediatric eye disease frequently leads to severe vision impairment and/or blindness, with long-lasting societal impact [1]. Gene therapy involves the transfer of genetic material to remove, replace, repair, or introduce a gene, or to overexpress a protein, which activity would have a therapeutic impact [2]. Over the last 10 years, gene therapy for biallelic RPE65-mediated inherited retinal dystrophy has been the subject of many clinical trials, leading to the first United State Food and Drug Administration (US FDA)-approved ocular gene therapy for the treatment of an inherited retinal disorder [3]. Voretigene neparvovec (VN, Luxturna®), administered by subretinal injection after 25-gauge vitrectomy, uses a non-replicating adeno-associated virus

(AAV) as a vector to transfer a functional copy of the RPE65 gene into the retinal pigment epithelium cells [4]. VN has shown to be well tolerated in humans, with encouraging results in ambulatory navigation, light sensitivity and visual field, mainly when administered early in childhood [5]. However, others promising approaches have been investigated [6]. Intravitreal injection of antisense oligonucleotides (AON), which induce persistent suppression of pathological RNA transcripts by exon skipping, has shown improvement in visual acuity at 3 months without serious adverse effects in CEP290-Leber congenital amaurosis [7]. Innovative CRISPR-based genome editing technique is another exiting approach currently evaluated for CEP290-Leber congenital amaurosis [8]. The ongoing clinical trial evaluates the safety, tolerability and efficacy of single escalating doses of EDIT-101, a novel gene editing product designed to eliminate the mutation on the CEP290 gene, administered via subretinal injection [9]. However, various congenital disorders already exhibit severe developmental defects or cell loss at birth, limiting the potential for viral gene therapy [10]. Thus, mutation-independent strategies seem promising to maintain cell survival or restore visual function. Optogenetic therapies deliver light-activated ion channels to surviving retinal cell types (for instance bipolar cell and retinal ganglion cells), restoring photosensitivity. Partial functional recovery has recently been reported in a patient with advanced non-syndromic retinitis pigmentosa after optogenetic therapy.The treatment combined the injection of an optogenetic vector and the use of light-stimulating goggles. The patient was able to perceive, locate, count, and touch various objects using the vector-treated eye alone while wearing the goggles. Other mutation-independent strategies tested in mouse models of retinal degeneration aimed to promote photoreceptor cell survival, as CRISPR-mediated knockdown of the key transcription factor Neural Retina Leucine zipper (Nrl), or viral-mediated expression of the rod-derived cone viability factor (RdCVF). Whether these strategies will translate into long-lasting restoration of retinal function in humans still remains to be determined.

Finally, beyond retinal function, ataluren, a nonsense mutation suppression therapy, enables ribosomal read-through of mRNA containing premature termination codons, resulting in production of a full-length protein. Postnatal administration of ataluren eye drops reverses congenital tissue malformation defects in Pax6Sey+/– mice. A Phase 2 clinical trial evaluating oral ataluren, that is already approved for the treatment of Duchenne muscular dystrophy, failed to meet its primary endpoint. An ophthalmic formulation has been recently assessed; this should encourage clinical trials using ataluren in congenital aniridia.

Restoring vision in children remains a challenge in ophthalmology. Gene therapy opens a promising field in constant development. Even though for most anterior segment diseases studies still relate to the preclinical stage, for inherited retinal disorders, translation has been reached, leading to the introduction of the first gene therapies in clinical practice.

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