Gene Therapy in Ophthalmology: Promise and Pragmatism

Dr. Muhammad Shaheer
Institute of Ophthalmology, Mayo Hospital Lahore.

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The aim of gene therapy is long lasting improvement or sure of a certain disease by transfer of genetic material to the patient. It may involve either of gene replacement, gene slicing, gene editing or addition.[1] Over the years, gene therapy has been extensively in practice with the use of adeno-associated virus (AAV) vectors for gene delivery and has been applied to neurodegenerative disease, cardiovascular disease, cancers and ocular disease.[2]

Eye is an excellent organ for gene vector delivery due to its immune privilege and direct visibility.[3] In 2017, "Voretigene Neparvovec" was the first gene vector to be approved by Food and Drug administration (FDA) for the treatment of RPE65 related inherited retinal dystrophy. Gene vector can be introduced into the eye by sub retinal injection after pars plana vitrectomy, intravitreal or suprachoroidal injections.[4]

Autosomal dominant retinitis pigmentosa (ADRP) is the most prevalent form of this disease and rhodopsin P23H (RHO-P23H) being the frequent mutant gene locus. Yan et al. developed sgRNA to specifically target the mutated rhodopsin RHO-P23H, subsequently resulting in knockdown in an ADRP mouse model induced by RHO-P23H mutation.[5] Choroideremia is an X linked recessive disorder due to mutations in CHM gene. Five clinical trials have been conducted on gene therapy for this disease with the first commencing in 2011. Adeno assisted virus vector (AAV) was introduced in subject's eyes after pars plana vitrectomy. Different strengths of AAV were used in these five trials. At 1 year, minimum gain of ETDRS letters was 2 while maximum gain was 17 letters in one of the trials. Only one patient diagnosed to have retinal tractions and stretching.[6,7]

Stargart's disease (STGD) is another inherited retinal genetic disorders caused by mutations in ABCA4. FDA passed adeno-associated virus (AAV) vectors are unable to carry large vector for some genes, such as ABCA4. Sun D and associates engineered a lipid nanoparticle having pH-sensitive amino lipid. This nano particle delivery system was assessed in mouse model. A2E is a main component of lipofuscin in ABCA4 gene and is responsible for phototoxic events. The A2E levels in mice were found to be significantly less than controls after treatment with multiple doses of nano particle delivery system.[8] Use of AAV for treatment of Leber Hereditary Optic Neuropathy is also under investigation. Results from ongoing trials show promising effects on both injected and fellow eyes of subjects.

Treatment Burden for neovascular age related macular degeneration (CNVM) is enormous globally in the form of anti VEGF injections. In the past decade, various clinical trails were initiated introduce drug into vitreous cavity through delivery systems which chronically expresses anti VEGF proteins thereby eliminating the need of anti VEGF injections. Optic and Infinity trials were performed on Non-Human subjects (Monkeys) and showed promising results in preventing expansion of (CNVM) lesions induced by laser while showing excellent safety profile at the same time.[9]

In the context of corneal gene therapy, AAV2

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Correspondence: Muhammad Shaheer
Associate Professor, Institute of Ophthalmology, Mayo Hospital Lahore.
Email: mshaheer212@gmail.com
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serotype was investigated for its efficacy in rabbit cornea. In Vivo gene delivery to rabbit cornea was successful suggesting positive prospects. Later on AAV5 sero type was injected in rabbit cornea and resulted in significant decrease in corneal haze and fibrosis, without any reports of any immunogenic or toxic immune response against it.[10]

Despite the promise and futuristic value, gene therapy in ophthalmology is currently limited to specific gene mutations, requires genetic testing and molecular diagnosis along with cold chain and strict regulatory oversight. Establishing a national registry for inherited disease including those of ocular nature, introducing affordable genetic testing and training of ophthalmologists in clinical genetics is need of the hour. Given the disease burden of Pakistan, preventable or treatable causes of blindness (Cataract, diabetic retinopathy and glaucoma) should be the top priority. However, due to high consanguinity and its direct genetic consequence (inherited retinal diseases), gene therapy becomes a strategic and equitable treatment/prevention option.

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