Is Gene Therapy the Game-Changer for Autosomal Recessive Deafness 9?

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Dear editor! One of the most challenging forms of hearing impairment is autosomal recessive profound prelingual deafness (DFNB9), which makes up over 80% of all congenitally occurring hearing loss cases (1). Otoferlin protein, encoded by the OTOF gene, is located at the inner hair cells, which mediates signal transduction for proper sound propagation. The OTOF gene mutations impair the physiological otoferlin function and account for almost 1–8% of all the DFNB9 cases (2). Currently, there are no medical therapies available to combat this disorder, and in this critical context, adeno-associated virus (AAV) serotype 1 carrying a human *OTOF* transgene (AAV1-hOTOF) may offer promising results.

AAV1-hOTOF is an experimental gene therapy intended to treat DFNB9. It transports the functional copy of the OTOF gene to the hair cells via an adenovirus vector. This enables the hair cells to produce newly functioning otoferlin protein, thereby regaining proper signal transduction and sound propagation.

A groundbreaking clinical trial, recently published in The Lancet, evaluates the efficacy and safety of this AAV1-hOTOF gene therapy for restoring hearing in patients with DFNB9. This first-of-its-kind trial demonstrated that AAV1-hOTOF showed excellent results and helped in reclaiming significant functional hearing in all the patients enrolled in the trial (3). Furthermore, along with enhanced hearing, gene therapy also assisted in improving speech perception in the patients. In addition to its increased efficacy, gene therapy had a favorable safety profile, with no reports of serious adverse events or drug-limiting ototoxicity (3). These findings of a successful response to gene therapy are in line with the case report by Qi et al., which also showed that AAV1-hOTOF helped restore substantial hearing in two children (4).

In South Asia, 1.62 out of every 1000 newborns suffer from congenital hearing loss, making it one of the most prevalent chronic pediatric illnesses (5). Due to the unavailability of any medical intervention, DFNB9 goes untreated, substantially affecting the quality of life of patients. However, with the introduction of gene therapies like AAV1-hOTOF, there is newfound hope for these patients. This pioneering therapy may completely eradicate DFNB9 and significantly enhance auditory function, providing a viable substitute for cochlear implants and conventional hearing aids. More clinical trials assessing larger patient populations are warranted to provide greater evidence for the effectiveness and tolerability of this therapy.

Keywords: autosomal recessive deafness 9; AAV1-hOTOF; congenital hearing loss; Asia

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