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Interdisciplinary MEDICINE

Clinical practice guidelines for gene therapy to treat hereditary hearing loss

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Abstract

Hereditary deafness is a common neurosensory disorder, and 148 non-syndromic deafness genes have been identified to date. Gene therapy has been used to treat a variety of genetic diseases, but no gene therapy drug for hereditary deafness has been approved for clinical use. At present, several clinical trials of gene therapy for hereditary deafness are underway. However, few normative documents have been issued to guide the standardization of gene therapy for hearing loss, and this document is the first global gene therapy guideline for hereditary hearing loss. The guidelines were jointly developed and drafted by experienced audiologists, virologists and biologists who are vigorously involved in inner ear gene therapy research in the Hearing,

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Speech and Communication Subsociety of Biophysical Society of China, Audiology Development Foundation Of China and Audiology Subsociety of Jiangsu Medical Association. These guidelines cover preclinical research and clinical practice of gene therapy for hereditary deafness, including indications, key points of pre-clinical research, patient selection criteria, pre-clinical preparation, drug efficacy, drug safety evaluation criteria, ethical review, etc. We hope that the guidelines will promote the standardization of clinical practice related to gene therapy for hereditary deafness in China and around the world.

KEYWORDS
clinical practice, gene therapy, guideline

1 | INTRODUCTION

Hearing loss is the most prevalent sensory deficit worldwide. Gene mutations are one of the main causes of congenital deafness, and mutations in more than a hundred genes are associated with non-syndromic deafness (https://hereditaryhearingloss.org; updated on January 12, 2024). Current clinical treatments generally involve assistive devices such as hearing aids and cochlear implants, but these methods have limitations in practical use. Several studies have demonstrated that hearing function can be successfully restored by adeno-associated virus (AAV)-mediated gene therapy in animal models of genetic defects, such as *Otof*, *Tmc1*, and *Syne4*-deficient mice.[1–7] Currently, AAV-mediated gene therapy for genetic deafness is being tested in clinical studies, focusing on autosomal recessive deafness 9 (DFNB9). There are five clinical trial registrations of gene therapy for DFNB9. One is registered in the China Clinical Trials Registry (ChiCTR2200063181) and four are registered in Clinicaltrials.gov (NCT05788536, NCT05821959, NCT05901480, NCT06025032). In addition, two Chinese clinical studies have reported the effectiveness of gene therapy in DFNB9 patients.[8]

DFNB9 is caused by mutations in the *OTOF* gene, and according to the report on Hearing Health in China (2021), the mutation rate in *OTOF* is as high as 41.2% in Chinese infants with auditory neuropathy. Several studies have already demonstrated that delivery of full-length *OTOF* using dual AAV vector (AAV-*OTOF*) restores hearing function in *Otof*-deficient mice.[1–4,9] We also showed the efficacy and safety of AAV-*OTOF* in *Otof*-deficient mice and cynomolgus macaques.[1] Subsequently, in collaboration with several well-known hospitals in China, we conducted and completed a clinical trial of AAV-*OTOF* therapy in several DFNB9 patients with profound or complete deafness. This therapy successfully restored the hearing of patients to almost normal levels and was shown to be well tolerated and safe.[8] Based on this, Zhongda Hospital affiliated to Southeast University, together with several other well-known hospitals in China, discussed and formed the guidelines on the clinical aspects of gene therapy for hereditary deafness (Figure 1).

2 | NATURAL HISTORY STUDY IN PATIENTS WITH HEREDITARY DEAFNESS

A detailed study of the natural history of a particular form of inherited deafness is needed to confirm that the appropriate patients are enrolled and to determine the time window for treatment. Patients should undergo physiological and behavioral assessments of auditory and vestibular function, including the assessment of patients' hearing, balance and speech perception. Patients and their parents or legal guardians should fill out questionnaires in order to collect information on epidemiology, quality of life, auditory and speech development, and health resource utilization. As examples, two natural history studies of deafness caused by mutations in the OTOF and GJB2 genes are available on the Clinicaltrials.gov website (NCT06019481 and NCT05402813, respectively).

3 | AAV PRODUCTION FOR CLINICAL USE

The AAV drug should be tested prior to clinical use,[10] including indication, titer, and purity. It is also necessary to test the infection titer and capsid integrity, and the AAV release testing should include the empty capsid rate and titer. Safety testing should include testing for the presence of microorganisms, mycoplasma, endotoxins, etc. In addition, the plasmids for AAV production used in clinical

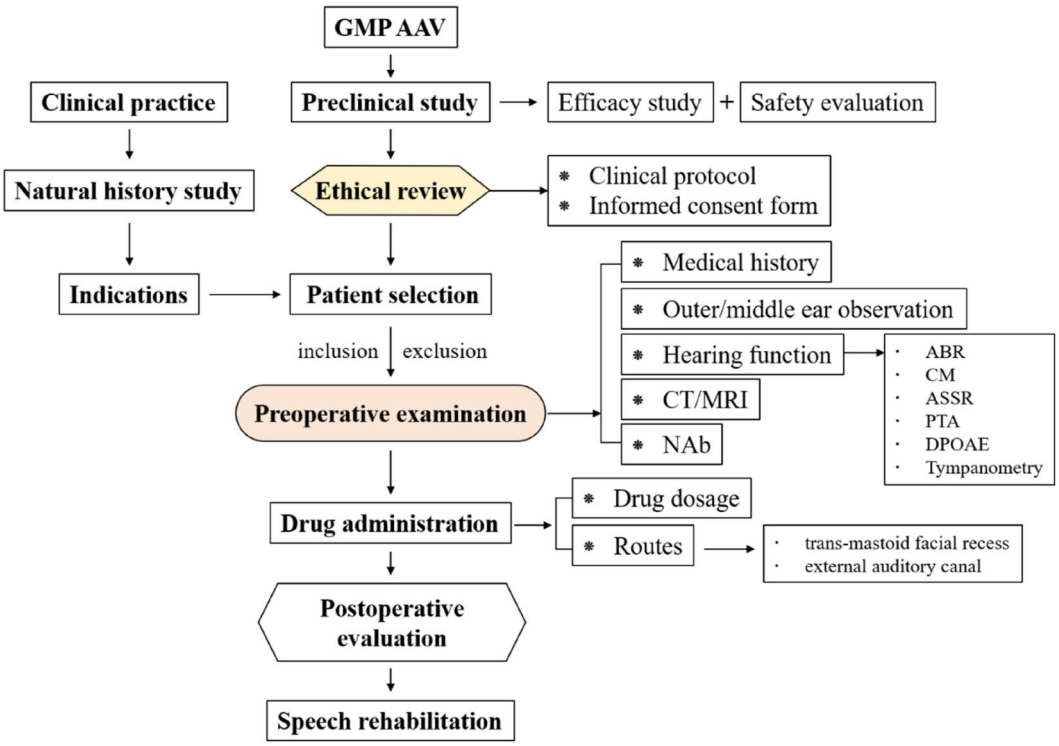

FIGURE 1 Flowchart of gene therapy practice for the treatment of hereditary hearing loss.

practice must meet the criteria of the good manufacturing practice of medical products (GMP). A two-level cell bank, master cell bank and working cell bank, should be established, and the characteristics should meet the requirements of the pharmacopeia in various countries. Moreover, the source, history, cell passages, and bacterial banks should be clearly described and traceable.

4 | ETHICAL REVIEW

As an advanced therapy, the benefits and risks of gene therapy must be adequately and thoroughly studied. For a specific form of genetic deafness, the effectiveness of gene therapy needs to be studied in animal models that mimic the human disease, and systemic safety data should be collected in non-human primates and reviewed by the ethics committee before beginning clinical research. It needs to be noted that clinical trials need to fully respect the right to informed consent of patients and/or guardians.

4.1 | Preclinical studies

Before the clinical application of gene therapy, complete preclinical efficacy and safety studies in animal models are required to allow for ethical review and to adequately assess the benefit-risk relationship of the therapy in patients and to guide clinical practice.

4.1.1 | Animal models

(1) Mouse models: Mice are used in short- and long-term efficacy studies of gene therapy drugs. It is necessary to construct genetically engineered mice that closely mimic the natural course of human hereditary deafness.
(2) Non-human primates: Cynomolgus macaques of both sexes aged 3–7 years can be used as experimental subjects for safety studies of the gene therapy drug.

4.1.2 | Efficacy studies

The time window for treatment needs to be determined, so the efficacy of gene therapy in mouse models should be assessed at different ages.

4.1.3 | Safety evaluation

(1) Referring to the surgical standard of cochlear implantation, the round window is exposed via the mastoid-facial recess and the gene therapy drug is injected into the inner ear of non-human primates, such as cynomolgus macaques, through the round window membrane.[1] Routine care, antibiotic administration, and local wound cleaning are performed for 7 consecutive days after surgery.

(2) Non-human primates injected with gene therapy drugs must be subjected to long-term observation, including general clinical observation, audiological examination, routine blood tests, blood biochemistry, pharmacokinetics, neutralizing antibodies (NAbs) against AAVs, and pathological examination.

4.2 | Contents of ethical review

The contents of the ethics application usually include the treatment protocol, the informed consent form, the drug efficacy report, and the drug safety report. The possible benefits and potential risks of the therapy must be fully explained to patients before proceeding to clinical practice.

5 | CLINICAL PRACTICE OF GENE THERAPY FOR DEAFNESS

5.1 | Indications

The gene therapy described in the guidelines is suitable for patients with non-syndromic inherited deafness caused by single gene mutations.

5.2 | Patient selection criteria

5.2.1 | Patient age

The minimum age of patients is recommended to be over 1 year old or to be similar to that of patients who are eligible for a cochlear implant. The maximum age needs to be fully evaluated based on the type of deafness and the patient's natural history.

5.2.2 | The patient should meet all of the following criteria

(1) The patient should have a definitive diagnosis of monogenic hereditary deafness by two or more clinical geneticists. The types of deafness are identified according to the guidelines for the interpretation of genetic variation developed by the American College of Medical Genetics and Genomics, the Association of Molecular Pathologists, and the College of American Pathologists.
(2) The cochlear structure of the patient should be intact. Diagnostic approaches usually include high-resolution computed tomography of the transverse/coronal cross-section of the temporal bone or magnetic resonance imaging (MRI) of the inner ear, cochlear microphonics (CM), and distortion product evoked otoacoustic emissions (DPOAE).
(3) Patients with severe, profound, or complete deafness are recommended for priority. 2021 WHO hearing loss classification criteria is used to assess the hearing loss (Table 1).

Severe hearing loss	65 dB ≤ threshold <80 dB
Profound hearing loss	80 dB ≤ threshold <95 dB
Complete hearing loss	≥95 dB

5.2.3 | Patients are ineligible for gene therapy if they have any of the following condition

(1) Having previously received any type of gene therapy in the inner ear or other tissues.
(2) Deformity of the inner ear.
(3) Bilateral cochlear implantation.
(5) High titers of NAbs against AAV serotypes used in gene therapies.
(6) Severe allergic reaction to any component of the gene therapy drug (NCI-CTCAE 5.0 grade ≥3).
(7) Ear infection or other infection.
(8) Insensitivity or allergy to narcotic drugs.
(9) Other criteria determined by the clinician to be inappropriate for gene therapy.

5.3 | Preoperative examination of patients

Before treatment, the medical histories of the patients need to be collected. Patients also need to undergo a variety of clinical examinations, including outer and middle ear structure, auditory function, CT or MRI of the ear, and Nab measurements in serum. Details are shown in Table 1.

5.4 | Drug dosage and routes of administration

5.4.1 | Volume and dosage

(1) According to previous studies, the safe volume is up to 60 μL at an injection rate of 20–100 nL/s.[8]
(2) The safe dose is variable and needs to be first established in mice and non-human primates.[1] Reasonable judgment is made according to the preclinical data in animals.

TABLE 1 Preoperative examination indexes and their intended aims.

Items	Indicators	Aims
Medical history	Family history: Family history of hearing Patient's personal history: History of hearing, systemic (including ear) surgery, hearing aid use, unilateral cochlear implantation, other ear diseases, allergies, other systemic diseases, mental illness, etc.	To grasp the patient's history as a whole and to make a preliminary judgment on whether gene therapy is a potential treatment
Outer/middle ear observation	Inflammation, deformity, trauma, tingling embolism, etc.	To eliminate conductive hearing loss
Hearing function	Auditory evoked potential: (1) Click-ABR, tone-burst ABR, CM, and ASSR (2) For patients >5 years old, pure tone audiometry (PTA) is routinely performed. The alternative methods include behavioral observation, visual reinforcement audiometry, and game audiometry (3) DPOAE (4) Tympanometry	A comprehensive assessment of the patient's hearing will guide clinicians to determine whether the patient meets the criteria for gene therapy
Imaging in otology	CT or MRI	To rule out abnormal ear structures
NAb	No NAbs against AAV capsid in serum	A positive result could interfere with the efficacy of gene therapy

Abbreviations: AAV, adeno-associated virus; ABR, auditory brainstem response; ASSR, multifrequency auditory-steady state responses.

5.4.2 | Route of administration

According to previous studies, round window membrane injection is preferred. Two routes can be used to expose the round window membrane, namely through the transmastoid facial recess[8] or through the external auditory canal.[11] With either method it is important to note the following.

(1) Inner ear drug delivery through the round window is a very delicate procedure that is prone to rupture of the round window membrane, thus exacerbating the hearing damage. This surgery requires the surgeon to be very careful.
(2) Round-window injection using an otomicroscope is recommended because it can provide a clearer view of the round window membrane.

5.5 | Surgery

The patient should be treated with glucocorticoids for 3 days before surgery to reduce the immune response caused by the AAV drug. The surgical preparation, including anesthesia, conventional surgical drugs, sterile barrier environment, sterile instruments, and sterile equipment, is similar to that of cochlear implantation. The operative procedure (except for the round-window injection) and post-operative care are also the same as for cochlear implantation.

5.6 | Postoperative evaluation

The patients need to undergo hearing and clinical safety examinations at a predetermined time point after surgery.

1. Safety indicators include vital signs and physical examinations, routine blood tests, blood biochemistry, coagulation function, and urine routine. Blood and urine samples are usually collected 1–3 days before surgery, 1–3 days after surgery, 1 week, and monthly in the first year. Follow-up examinations are determined by the clinician.
2. According to clinical trials and our studies in mice and non-human primates,[1,8] AAV can rapidly spread to the blood after cochlear injection, which causes an increase in NAbs. Therefore, it is necessary to perform pharmacokinetic studies of AAV. The qualitative and quantitative QPCR method is used to quantitatively analyze the AAV DNA distribution. Similarly, NAb detection methods for specific AAV capsids also need to be developed. NAb detection is required within 1 month before surgery. The exzamination could be conducted at 3 days, 1 week, 2 weeks and monthly after surgery within 1 year. Follow-up examinations are determined by the clinician.
3. The audiological examinations include click auditory brainstem response (ABR), tone-burst ABR, CM, ASSR, pure tone audiometry, DPOAE, and tympanometry, which should be compared with pre-operative values. These audiological examinations are required

within 1 month before surgery. The first hearing test is recommended as early as 2 weeks after surgery, then at 1 month, 2 months, 3 months, 6 months, 9 months, 12 months after surgery. The postoperative examination time points of various hearing indicators are provided as a general guideline and should be adjusted based on individual patient circumstances.

5.7 | Speech rehabilitation

After treatment, it is critical to provide speech rehabilitation training. Speech rehabilitation training is a comprehensive intervention program that requires the guidance and participation of professional speech therapists and auditory experts and the full participation of the patient's family members. Through systematic rehabilitation training, patients can make significant progress in hearing and speech, thus improving their quality of life and social skills.[12,13] The training should include auditory training, language and communication training, cognitive training, and social adaptability training.

6 | SUMMARY

Gene therapy for hereditary deafness is now moving from bench to bedside, and we have published the clinical results of using gene therapy to treat DFNB9 deafness.[8] This clinical trial has accumulated rich experiences in AAV-mediated gene therapy for deafness, including AAV molecular design, animal experiment protocols, clinical surgical methods, and other aspects. Therefore, it is a good time to publish the guidelines, which have significance as a reference for gene therapy for a variety of hereditary deafness types. The guidelines will also promote the standardization of gene therapy for deafness and promote the development of the field.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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