Gene therapy

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Background

Gene therapy is an alternative treatment for genetic lung diseases, especially monogenic disorders such as cystic fibrosis. Only a small number of active gene therapy vectors need to reach their target cells to produce an improvement in CF lung disease, but the greatest challenge is to find an ideal vector able to deliver the wild-type cystic fibrosis transmembrane conductance regulator (CFTR) gene to airway epithelial cells. To date, the limited efficacy of gene transfer vectors and extra- and intra-cellular barriers have prevented the development of a gene therapy-based treatment for CF.

Predominantly used in the pioneering days of CF gene therapy, adenovirus-based vector has been progressively abandoned in the last decade due to its poor transduction efficiency in human airway epithelial cells and to its re-administration inability. As potential alternatives, adeno-associated virus (AAV) and lentivirus-based vectors were assessed. However, further data are needed to evaluate their feasibility. On the non-viral side, parallel work has been made regarding the formulation of other vectors (cationic liposomes).

To coordinate gene therapy research the UK Cystic Fibrosis Gene Therapy Consortium was founded in 2001 and a programme has been developed with two products (Wave 1 based around liposomal gene transfer, and Wave 2 focused on a novel virus). In the first part patients were enrolled in June 2012 with results noy yet available (Armstrong DK, 2014).

Prenatal gene therapy is a potential alternative to gene transfer to fully developed lung (Keswani SG, 2012) and pre-clinical studies will surely benefit from novel animal models, such as CF pigs and ferrets (Oakland M, 2012).

Recently (Bangel-Ruland N, 2013) has been hypothezed that CFTR-mRNA transfection could be a novel alternative for gene therapy to restore impaired CFTR function. A phase Ib clinical trial was scheduled (Henig N, 2015).

In 2013 Schwank G, 2013 et al. published data on CRISPR/Cas9 genome editing system to correct the CFTR locus by homologous recombination in cultured intestinal stem cells of CF patients. The corrected allele resulted expressed and fully functional as measured in clonally expanded organoids. This study provided proof of concept for gene correction by homologous recombination in primary adult stem cells derived from patients with a single-gene hereditary defect.

Issues

Identification of the most suitable vector for efficient and safe CFTR gene transfer to airway epithelia.

Identification of alternative approaches for CFTR gene defect correction.

Assessment of sensitive and specific surrogate biomarkers.

Assessment of gene therapy impact on clinical outcomes (respiratory condition, quality of life, survival, nutritional parameters, sputum, radiological features).

Assessment of bone marrow-derived hematopoietic or mesenchymal stem cell strategy feasibility.

Assessment of prenatal gene therapy feasibility.

What is known

One CDSR (Lee TWR, 2016) on topical CFTR gene replacement for CF lung disease and including 4 studies concluded that till now there is no evidence of efficacy for viral-mediated gene delivery.

One CDSR (Perry LA, 2016), on topical CFTR gene replacement for CF lung disease included four randomised controlled studies met the inclusion criteria for this review, involving a total of 302 participants lasting from 29 days to 13 months. The included studies differed in terms of CFTR gene replacement agent and study design, which limited the meta-analysis. One study of liposome?based CFTR gene transfer therapy demonstrated some improvements in respiratory function in people with CF, but this limited evidence of efficacy does not support this treatment as a routine therapy at present. There was no evidence of efficacy for viral?mediated gene delivery. Future studies need to investigate clinically important outcome measures.

One RCT (Caplen NJ, 1995) demonstrated that cationic liposome agents, as gene transfer agents, were safe in 9 CF patients.

Unresolved questions

There is the need to study all the indicated issues, even if, given the features of gene therapy, RCTs may not always be feasible.

A study (CTIS2023-503281-23-00, 2024) to test how well BI 3720931 is tolerated and whether it improves lung function in people with cystic fibrosis (LenticlairTM 1) is ongoing

A Cochrane protocol (Addy C, 2026) is ongoing and will ivestigate nucleic acid?based therapies (NABTs) (including variant?specific antisense oligonucleotide therapies, variant?agnostic mRNA, and DNA?based gene therapies) in comparisons with either no treatment, a placebo or a different NABT. Critical outcomes will be: Quality of life (QoL) (Total score, Respiratory domain). FEV1. AEs. Survival. Pulmonary exacerbations. Important outcomes: Hospitalisation. School or work attendance (i.e. number of days missed). Extra courses of antibiotics (measured as time to the next course of antibiotics and the total number of courses of antibiotics), Sweat chloride. FVC, Lung clearance index. Radiological measures of lung disease. Microbiology: Acquisition of CF?associated pathogens, Eradication of CF?associated pathogens. Nutrition and growth: Weight, Body mass index (BMI), Height.

Keywords

Gene Transfer Techniques;