A randomised, double-blind, placebo-controlled trial of repeated nebulisation of non-viral cystic fibrosis transmembrane conductance regulator (CFTR) gene therapy in patients with cystic fibrosis

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Cystic fibrosis (CF) is an inherited disease that significantly shortens life because of severe lung disease. Only one treatment aimed at the underlying cause is currently available and this is suitable for only the 4% of patients who have specific types of gene mutations; standard care for all other patients targets the symptoms of the disease rather than the cause.

Gene therapy aims to insert a normal copy of the gene back into the lungs' cells and restore function. In the UK CF Gene Therapy Consortium we have (1) identified the best vector with which to gain cell entry; (2) designed a piece of genetic material capable of safely expressing the missing protein for a prolonged duration; (3) found out how we can deliver this to the lungs using a clinical nebuliser; (4) tested safety in two animal models; and (5) confirmed a safe dose in a single-administration trial.

In this trial, CF patients (aged ≥ 12 years) randomly received gene therapy or placebo every month for 1 year. The primary outcome was a change in lung health, measured by a standard breathing test [forced expiratory volume in the first second (FEV₁)]. In addition, we included a number of secondary and safety outcomes.

One hundred and sixteen patients received at least nine doses and were analysed for efficacy. After 12 months, a statistically significant, but modest, difference was observed between the two groups for FEV₁; this was supported by trends in other outcomes. Effects were independent of gene mutation, age and sex. There were no significant safety concerns.

We suggest the results reported here provide proof of concept that repeated administration of CF transmembrane conductance regulator (CFTR) gene therapy can alter clinically relevant outcomes, providing another step along the path of translational CF gene therapy.
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