Gene therapy for children with cystic fibrosis—who has the right to choose?

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It may be unethical to deny children with cystic fibrosis access to ethically approved clinical trials from which they might benefit

Despite advances in nutritional management, aggressive antibiotic usage, and physiotherapy, cystic fibrosis (CF) remains a life limiting illness with high morbidity that imposes considerable burdens on children and families.¹ Although survival to 40 years is predicted for children born in 1990s, the median age of death in 2003 was 24.2 years (UK CF Trust database).

The pathophysiological features of CF are produced by a defective gene on chromosome 7, resulting in the defective production of a protein that regulates cellular ion transport. Defective ion transport is thought to lead to increased mucus viscosity (sticky sputum), with poor airway clearance, recurrent bacterial infection, lung damage, and death.

Gene therapy (GT), the insertion of a normally functioning gene into deficient host cells using a suitable vector, is a potential treatment or cure for diseases produced by single gene defects—for example, CF. Gene therapy does, however, have potential or actual risks, leading many to suggest that evidence of efficacy in adults should be demonstrated before trials are conducted in children. Many serious diseases in adults such as CF have their onset in childhood. If early treatment provides greater hopes of benefit, children may be more appropriate targets for GT in CF than adults. It may be unethical to deny them access to properly constructed, ethically approved clinical trials from which they might benefit.

Since research in children should be scientifically valid, in the child's best interests, and the subject of valid consent, this article will consider these parameters in relation to trials of GT in children with CF. Because of the importance of consumer participation in the design of research we present the results of a questionnaire about GT trials delivered to parents of CF children in our unit.

SCIENTIFIC VALIDITY OF GENE THERAPY IN CHILDREN WITH CF

Topical delivery of the gene to the airways is the current method of

delivering GT in CF. A variety of vectors including viruses,² liposomes,³ and other chemicals^{4–5} have been used. Viruses are efficient at transferring genes but produce inflammatory responses that may limit their repeated use, whereas liposomes are relatively safer but less effective. Over 30 trials of GT (mainly in adults) have demonstrated that gene transfer with correction of the ion transport defect can occur.⁶ None have shown definite clinical benefit, but there may be significant differences between the lungs of adults and children that explain this. Children with CF are born with normal lungs but rapidly develop lung inflammation⁷ and may have abnormal lung function in the absence of respiratory symptoms.⁸ Adults, with even mild lung disease, are likely to have sufficient mucus in the lower airways to produce a physical barrier to effective gene transfer,⁹ making it impossible to obtain in vivo evidence of gene transfer. Similarly, adult patients may demonstrate an enhanced inflammatory reaction to gene transfer³ because their lungs have more inflammation present in the lower airway compared with children. Furthermore, adult and growing lungs may behave differently with regard to gene transfer, as demonstrated in animal models using different vectors.^{10–11} Therefore animal and human adult data may not provide relevant information about the safety, efficacy, or choice of vector for children.

Thus far clinical research with GT in CF has been mainly restricted to adults with established lung disease, where clinical response may be small and difficult to measure, rather than in the prevention of the onset of lung disease where measurable clinical benefits may be larger. This has important consequences for the logistics of trials. It would require enrolment of a large number of patients with established lung disease over a one year period to demonstrate any statistically significant difference in decline in lung function produced by GT. The numbers required to show a similar effect in younger

patients with milder lung disease are smaller, making the feasibility of successful completion of such a study more likely,¹² especially given the finite numbers of patients with CF. There would seem to be some scientific validity for the proposal to carry out GT in children.

BEST INTERESTS, BENEFITS, HARMS, AND RESPECT FOR AUTONOMY IN CHILDREN WITH CF

All medical research and treatment involving children must balance the competing duties to produce more benefit than harm and allowing the children to exercise as much self determination (autonomy) in decision making as they are capable of or want.

Adults are regarded as competent to assimilate, understand, retain, and weigh information about themselves and their condition and use it to decide whether they will take part in research. Many children lack these abilities but this cannot be assumed in the context of chronic illness when a child's experience may confer unexpected competencies not related to age.¹³ Parents have ethical and legal rights to make decisions on behalf of their child provided that they act in the child's best interests.

Deciding what constitutes a child's best interests includes balancing a wide range of physical and psychological benefits and harms. A number of professional bodies have issued guidance on this process in the context of research.^{14–16} The Gene Therapy Advisory Committee (GTAC) recommends that children should only be subjects when research is necessary to promote the health of the trial population, the research cannot be done in adults, and there is some possibility of therapeutic benefit. While the latter is difficult to demonstrate in innovative treatments such as GT it may be neither possible nor desirable to place limits on research that may have unquantifiable benefits.¹⁷ The Royal College of Paediatrics, Child Health (RCPCH) guidance, while acknowledging the principle that research should only be done on children if comparable research on adults cannot answer the same question, recognises that children have unique additional needs, and should be the benefactors of ethical research.

The risks and ethics of GT have recently been reviewed,¹⁸ one difficulty being defining potential risks. Gene transfer lacks the specificity of using pharmaceutical agents so its effects are less predictable. Moreover, experience with GT in children is largely confined to life threatening illnesses, such as

severe combined immunodeficiency (SCID), where no other therapeutic options exist. The development of leukaemia in three SCID children (with one death) treated with retroviral gene therapy, and the death of an adult following adenoviral gene therapy for ornithine transcarbamylase deficiency, are particularly concerning. Most side effects of GT in adults with CF have, however, been mild, including flu like symptoms, cough, and wheeze.³

While some risks are predictable—for example, wheezing following inhalation of genes and their vectors—others are not. We lack knowledge about all the risks associated with both the vector and the resultant gene expression. In the SCID trial the vector integrated near a cancer causing gene and the gene expression may have helped to transform the leukaemia causing cells.¹⁹ It is not clear why only some patients developed cancer, or the relevance of this finding to GT in CF. In SCID the site of gene delivery is systemic (to the haemopoietic system) whereas in CF it is topical, and the gene is unlikely to integrate with host DNA in the same way as it does in SCID. It may be argued that in the face of these unknown risks it would be unethical to propose clinical trials of GT in CF. Other less controversial therapies are available—for example, organ transplantation, albeit resulting in a significantly reduced normal life expectancy. They do, however, entail considerable burdens for children and their families and must be seen in the context of a life limiting progressive illness for which they do not provide a cure.

None the less we have accepted stem cell therapy and xenografting, which involve similar unquantifiable risks, subject to certain constraints that include long term follow up and data monitoring. We have also, in the context of children's cancer treatment, accepted that it may be ethical to store gonadal tissue in prepubertal children.²⁰

CONSENT AND ASSENT IN CHILDREN AND FAMILIES

All medical research requires valid consent of participants or a person able to consent on their behalf. To be valid, consent must be sufficiently informed and given freely by a person who is competent to do so. The difficulty of obtaining truly informed consent for research projects, especially those involving randomised controlled trials, acute medical situations, and children is well recognised.²¹ It is clear, however, that these difficulties should not necessarily preclude research that is in the best interests of the child.¹⁵

The information required to obtain consent for medical treatment is that which a prudent patient might want to make the decision in question. Arguably the information standard for innovative therapy/research should be that which a particular patient might want. Both children with CF and their parents are usually knowledgeable about their illness and may initiate discussions about GT.

Concepts of competence, as previously defined, are inextricably intertwined with information. The UN Convention of the Rights of the Child provides a child's right to information in a form that they can comprehend irrespective of their ability to make decisions.²² However, young children under 10 years may not be able to assent to research projects.²³ Competence to make decisions is based upon the child's ability to understand fully the nature and purpose of what is involved and the impact on their family.²⁴

The psychosocial dynamics of families with chronic illness are complex and may involve misunderstandings about the child's knowledge and understanding, mutual pretence (where both parties evade difficult issues), and misunderstanding of the social roles of the child and the family.²⁵ This means that children's participation in decision making may be limited. It has been suggested that a diplomatic negotiated approach may be helpful in overcoming this problem. Faced with a child's life limiting illness, parental desperation may lead them to accept significant risks on behalf of their child with little hope of benefit; they may feel coerced into accepting participation in research whose aims they do not truly comprehend.

Some of these difficulties may be overcome by considering consent for research as a dynamic process in which the duty of the researcher is to increase the competence of both parents and child by education, negotiation, and dialogue

Despite these difficulties, both scientists and gene therapy regulatory authorities have recognised the need to include children in gene therapy research and especially in research into the potential use of somatic cell gene therapy to cure serious diseases in children.²⁶ In a recently reported trial of adenoassociated virus gene therapy in CF, the age of enrolment was progressively reduced from 18 to 12 years following interim safety reviews.² The proposal for long term follow up of research subjects and adequate data monitoring would seem to be essential conditions for this type of therapy.

PARENTAL ATTITUDES TOWARD GENE THERAPY

Whilst scientists may argue that children should be included in gene therapy trials, there are no data to support the views of parents, who will need to give consent to their children participating in these trials. We therefore sought the opinion of parents of CF children on the question of conducting gene therapy trials in general and whether they would be willing to enrol their child/children in any such trial. The hospital ethics committee deemed formal ethical permission for this survey unnecessary. One hundred and sixty parents of children from our tertiary CF centre were sent an anonymised short questionnaire (Appendix 1). The response rate was 48.8%. Families who responded had a total of 80 children (48 female) with an age range of six months to 17 years. Eighty two per cent (64/78) of respondents felt that gene therapy was the most important area of research in CF, with 56% of respondents hoping for a cure; 31% expecting that it might improve symptoms but not cure the disorder; 10% hoping for both, and 3% not sure. Ninety nine per cent of respondents felt it was ethically sound for children to be given the opportunity to be involved in gene therapy trials provided that they were carefully run, with safety issues as the priority. Ninety one per cent of families stated that they would consider consenting to their child(ren) taking part in a CF gene therapy trial. Four per cent said they would not consider consenting and 5% of families felt unable to make such a decision.

Our small survey has several limitations. Although only 48.8% of parents responded, this is an expected response rate following first mailing of a postal questionnaire.²⁷ It is possible that responders felt more strongly about supporting gene therapy trials than non-responders and hence biased the results. Given the strongly positive responses received, however, it is likely that the majority of parents would still favour research if the response rate had been higher. A second limitation is that these results reflect parental views from a single centre. However, our centre is the second largest paediatric centre in the United Kingdom and looks after 187 patients from 17 different counties in the South East of England. Thus we believe that our population is heterogeneous and is likely to be representative of parents from other CF centres in the UK. Third, we were not explicit about the risks associated with gene therapy, which may have affected the responses to potentially value laden questions. We did not do this as we

were principally interested in evaluating whether parents would consider the idea of enrolling their children into a future gene therapy study. We accept that a parent's wish to consider enrolling their child into a study does not mean that they will actually consent after they have received a detailed explanation of the specific risks of gene therapy. Nevertheless, the positive responses suggest that our parents would consider recruiting their children into future gene therapy trials.

Although these data may support recruitment of children in future trials, children with CF and their parents are a vulnerable group who may be anxious to benefit from technological advances despite the risks attached. Scientists and clinicians have a moral duty to protect vulnerable groups from harm and to promote their competence without compromising their autonomy. This means that safety is a paramount consideration when designing clinical trials, otherwise we are in danger of exploiting this vulnerability. Promoting competence also involves a duty to raise public awareness and stimulate debate on controversial subjects such as GT in children, which is one of the main objectives of this paper.

CONCLUSION

Gene therapy in CF has progressed rapidly over the past few years. Six years ago we called for a rational dialogue between scientists, doctors, and laymen.²⁸ We believe that in the intervening years this has happened, largely through the efforts of regulatory authorities such as GTAC, and the results of our survey further support our view that we are ready for gene therapy trials in children with CF. As Kodish points out: "for too many years, children...have been therapeutic orphans, denied the benefits of clinical research".²⁹ The discussion and information in this paper may be helpful to gene therapy regulatory bodies when considering the design of future clinical trials.

APPENDIX 1

Questionnaire sent to parents of children with CF

1. Which areas of research do you feel are the most important in relation to CF?
  - (a) Gene therapy
  - (b) Finding new and more effective treatments other than gene therapy
  - (c) Both

2. From what you have read in the past, what hopes do you have, if any, for gene therapy in CF?

- (a) A cure
- (b) Effective treatment, which will improve but not cure
- (c) Not interested in gene therapy
- (d) No comment

3. How many children with CF do you have?

- (a) Boys: Girls:
- (b) Ages:

4. How is your child's general health at present?

- (a) Very well—no problems
- (b) Generally well, but requires additional antibiotics from time to time
- (c) Needs frequent courses of antibiotics and occasionally needs IV antibiotics
- (d) Needs intravenous antibiotics regularly

5. How much is your family's daily life affected by having CF?

- (a) No disruption, we lead a full and normal life
- (b) The treatments do interfere with normal life but only minimally
- (c) Our life is moderately disrupted by CF
- (d) It is impossible for us to lead a normal life because of CF

6. Do you think that it is ethically correct for children to be given the opportunity to be involved in gene therapy trials, if their families agree and if the trials are run very carefully?

- (a) Yes
- (b) No
- (c) No comment

7. If Great Ormond Street Hospital were to run a gene therapy trial, would you be willing to consider consenting to your child taking part?

- (a) Yes
- (b) No
- (c) Unsure

Please write additional comments here:

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CONTRIBUTORSHIP

SH and AJ originally discussed the idea of the paper. SAP developed and carried out the parental survey. VL contributed to the writing of the manuscript. AJ and SH are currently carrying out research in gene therapy toward a gene therapy trial in children with CF.

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