

## Gene therapy trials in the UK: is haemophilia a suitable 'model'?

UK Haemophilia Centre Doctors' Organisation Working Party\*

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**ABSTRACT – Gene therapy may be the next major advance for treatment of many diseases, and severe haemophilia (an inherited deficiency of coagulation factor VIII or IX) is a useful model. Progress in gene therapy has been slowed down following fatal multi-organ failure during an adenovirus vector trial for ornithine-transcarbamylase deficiency and two episodes of leukaemia in a retroviral vector trial for severe combined immunodeficiency trial. A small number of early haemophilia clinical trials are in progress or reported. This paper considers ethical and statutory issues related to gene therapy for severe haemophilia within the UK and how these can be addressed through a well-established national network of haemophilia centres. It is likely that these issues will be relevant to clinicians considering gene therapy for other diseases.**

**KEY WORDS:** adverse events, ethics, gene therapy, haemophilia, legislation

Gene therapy may be the next major advance for treatment of many diseases, and severe haemophilia (an inherited deficiency of coagulation factor VIII or IX) is recognised as a useful model.<sup>1,2</sup> The UK is an attractive country for haemophilia gene therapy trials because of national coordination through the UK Haemophilia Centre Doctors' Organisation (UKHCDO), centres experienced in performing clinical trials and the robust regulatory system. The UKHCDO wishes to collaborate with regulatory agencies to facilitate gene therapy in the UK and ensure the highest possible safety mechanisms.

### Clinical and scientific basis

Severe haemophilia is ideal for somatic gene therapy for clinical and scientific reasons. Although complications are avoidable with prophylactic treatment, this is invasive and has significant morbidity in young children. Coagulation factor replacement is expensive and supply uncertain. Previously, plasma-derived therapy resulted in transmission of HIV and hepatitis and patients now expect state-of-the-art

treatment. World-wide, most haemophiliacs have no effective therapy.

Haemophilia is caused by a single gene defect treatable by single gene addition. There is a wide therapeutic range of clotting factor levels; tissue-specific production of clotting factor is probably unimportant, and a small increase from baseline levels leads to a measurable and clinically significant benefit. Patients and families are well informed and likely to volunteer for studies. Those who treat haemophilia are experienced in performing clinical trials to high standards and follow-up will be good.

These advantages must be balanced against concerns about serious adverse events in recent trials.<sup>3,4</sup> Haemophilia is no longer a life-threatening disease and replacement therapy, if available, is safe and efficacious. Gene therapy may induce inhibitor development (allo-antibodies that inhibit FVIII/IX) and the antigenic stimulus may not be easily removed. Gene therapy in patients infected with HIV and hepatitis may interfere with the course of these diseases.

### Scientific, safety, research and ethical issues in human gene therapy trials in haemophilia

Gene therapy may be viewed as qualitatively different from other treatments, but from a broader perspective it is a natural progression in the application of biomedical science to medicine. Progress in gene therapy, however, has been slowed following fatal multi-organ failure during an adenovirus vector trial for ornithine-transcarbamylase deficiency,<sup>3</sup> and two episodes of leukaemia in a retroviral vector trial for severe combined immunodeficiency trial.<sup>4</sup> Over-zealous reporting and media interest in early studies in gene therapy have obscured their exploratory nature and heightened expectations. Research in gene therapy for haemophilia is now catching up. Five clinical trials involving 25 patients are in progress or completed with early reports available.<sup>1,2,5</sup> Dermal fibroblasts transfected by a FVIII vector using electroporation and reimplanted in the omentum led to a transient small FVIII increment.<sup>6</sup> An adeno-associated viral (AAV) FIX vector given

\* See end of paper for Working Party membership.

intramuscularly led to gene transfer confirmed by biopsy.<sup>7</sup> An AAV vector expressing a FIX minigene has been administered via the hepatic artery; vector DNA was transiently detected in semen.<sup>8</sup> A retroviral vector expressing B-domain deleted factor VIII given intravenously in severe haemophilia A led to some patients having measurable FVIII levels and decreased bleeding frequency.<sup>9</sup> A patient treated with a gutless adenovirus vector had a FVIII level rise above 1%. The study was suspended transiently following hepatotoxicity and thrombocytopenia. Expansion of pilot studies or modified protocols are inevitable but safety issues must be paramount.

### Scientific and safety issues

The following questions need to be answered:

- 1 Are the outcome measures of efficacy and risks clear and objective?
- 2 Adverse events have led to the suspension of clinical trials. Is the process for such adverse event reporting sufficiently robust to alert other investigators and the regulatory bodies in good time to take action?
- 3 Are there adequate data in relation to gene delivery and the host response to viral vectors from animal models to justify human studies?
- 4 Are there secure data that show absence of germ line modification? What are the implications of the transient appearance of vector in semen?<sup>7</sup>
- 5 If an adverse event occurred directly related to the production of factor VIII or IX, how would the transgene be switched off/removed?
- 6 Patients with HIV infection may have more adverse events than those who are uninfected and the natural history of the

## Key Points

**Severe haemophilia is a suitable disorder for somatic gene therapy because a small increase in coagulation factor level causes a substantial decrease in the frequency of bleeding episodes**

**Gene therapy trials in haemophilia are likely to be introduced in the UK soon because of the national coordination of care, the experience of haemophilia centres in performing clinical studies to a high standard, and the existence of robust regulatory systems**

**Unpredictable and serious adverse events in gene therapy trials for other diseases have occurred**

**There are significant ethical issues that must be considered before gene therapy trials are started**

**Gene therapy trials should be guided by protocols that are applicable to the majority of patients with haemophilia and it should not primarily be used as a model disease to develop techniques that are more applicable to other commercially more attractive diseases**

disease may be altered. Will inclusion of immunosuppressed patients lead to a false sense of security with regard to the chance of anti-FVIII antibody production?

- 7 In hepatic gene therapy, will hepatitis C virus (HCV) infection preclude inclusion?
- 8 Will entry into one trial preclude future treatments with potentially better therapies? If so, in which patient groups would this be ethically acceptable?
- 9 Should patients be allowed to undergo multiple protocols sequentially?

### Ethical issues

Adults can give informed consent and should be the initial subjects. It is likely, however, that children will be enrolled as they will be free of HIV and HCV infection and benefit more from avoiding intravenous prophylactic infusions 3–4 times a week. Even given the provisions of the Children's Act 1989 in relation to consent (ie assent being obtained from the child and consent by a parent on behalf of the child), is it ethical to enrol children when long-term side effects are unknown and long-term follow-up is required?

### Regulation of gene therapy in the UK

Regulation of human gene therapy research is subject to additional regulation compared with other trials. Central to this process is the Gene Therapy Advisory Committee (GTAC).

#### Gene Therapy Advisory Committee

GTAC was established to oversee gene therapy research in the UK following the recommendations of the Clothier Committee on the ethics of gene therapy.<sup>10</sup>

GTAC's terms of reference are to:

- advise on proposals for gene therapy research on humans on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks
- work with other agencies including local research ethics committees, the Medicines Control Agency (MCA), the Health and Safety Executive and the Department of the Environment
- provide advice to health ministers on gene therapy research.

GTAC stipulates that all gene therapy research and recruitment into trials must take place under strict rules set out by and only after review of clinical protocols by GTAC.

#### Local Research Ethics Committees (LRECs) and GTAC

Gene therapy research must comply with standard LREC review and be seen to be conducted in a way that is beyond reproach. GTAC complements this by undertaking an authoritative and enabling review of protocols to establish whether a proposal meets accepted ethical criteria.

### Other bodies with responsibilities in gene therapy research

Other bodies have responsibilities, some statutory, in relation to gene therapy research. GTAC notifies the relevant LREC, the MCA and the appropriate NHS body of its decisions.

- The MCA regulates medicinal products and applications for use in clinical trials according to the Medicines Act 1968 and Directive 65/65/EEC. Gene therapy research comes under the requirements applying to clinical trials and consideration of application for a product licence.
- The Health and Safety Executive (HSE) is concerned with the protection of health from ill-effects of activities within the workplace. Genetic modification and use, culture and disposal of genetically modified cells or organisms, under conditions of containment, are subject to the control of HSE under the Genetically Modified Organisms (Contained Use) Regulations 1992.
- The Department of the Environment may need to issue consent if the research employs viable genetically modified cells or organisms that spread into the environment (for example, as a consequence of the use of viable viral vectors) under the provisions of the Genetically Modified Organisms (Deliberate Release) Regulations 1992.
- The NHS body, under whose responsibility the research would take place, decides whether a research proposal should proceed.

### UK national haemophilia gene therapy register

Gene therapy protocols used in the UK for the treatment of haemophilia will be registered with GTAC, but UKHCDO should also be aware of their existence and each trial should be registered with the organisation. Patients who have entered a gene therapy trial should have this information recorded on the national haemophilia database (as with any conventional haemostatic treatment) to enhance safety, improve adverse reporting and ensure long-term surveillance of subjects. This will be important if patients are exposed to multiple gene therapy protocols, move area or unexpected complications develop from different protocols after many years.

### Conclusions

Haemophilia offers an ideal model for the development of gene therapy, but it is recognised that, from a commercial point of view, disorders such as cancer and cardiovascular disease will be more attractive. Once developed, gene therapy protocols should

be applicable to most, if not all, people with haemophilia including those with hepatitis and HIV. It is important that haemophilia is not used simply as a model for gene therapy, but experience gained from such studies will potentially benefit patients with a wide range of other conditions.

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### Members of the UKHCD Working Party

**CA Ludlam** (Chair), Department of Haematology, Royal Infirmary of Edinburgh; **KJ Pasi**, Division of Haematology, University of Leicester ; **PW Collins**, Department of Haematology, University of Wales College of Medicine; **PHB Bolton Maggs**, Department of Haematology, Royal Liverpool Children's Hospital; **AM Cumming**, Department of Haematology, Manchester Royal Infirmary; **G Dolan**, Department of Haematology, Queen's Medical Centre, Nottingham; **A Fryer**, Department of Clinical Genetics, Royal Liverpool Children's Hospital; **FGH Hill**, Department of Haematology, Birmingham Children's Hospital; **IR Peake**, Division of Genomic Medicine, University of Sheffield; **D Perry**, Haemophilia Centre and Haemostasis Unit, Royal Free Hospital; **M Smith**, Haemophilia Centre, St Thomas' Hospital, London.