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Clinical trials in gene therapy: Ethics of informed consent and the future of experimental medicine

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As the field of gene therapy has matured, data from several new clinical trials have been published in high impact journals, such as *New England Journal of Medicine*. This has meant a correspondingly high interest by the media. Data from new clinical trials in gene therapy, for example, for the treatment of Leber's congenital amaurosis (LCA) [1-3] and Parkinson's disease [4], were published for the first time, and clinical trials that were initiated this year for various cancers, such as brain tumors, multiple myeloma, breast, head and neck, prostate and ovarian cancer, among others, are ongoing. The outcome of gene therapy clinical trials in 'bubble boys', who were treated for X-linked SCID 1(SCID-Xl) has continued to be monitored for the development of additional cases of leukemia, although no new cases have been reported beyond the five already identified in the French trial and one in the British trial [5,6].

The original hope that gene therapy could cure otherwise untreatable, inherited genetic diseases has been rekindled by a gene therapy clinical trial for LCA. In this disease, retinal photoreceptors degenerate at birth or very soon thereafter, and the retina is replaced gradually by scar tissue as photoreceptor death advances. Patients with LCA usually become blind sometime in their mid to late teens and treatment to prevent, delay or cure the blindness is not currently available. Maguire *et al* (Scheie Institute, University of Pennsylvania, USA) reported the treatment of three patients with mutations in the retinal pigment epithelium (RPE)65 gene; adeno-associated virus (AAV) serotype 2 vectors encoding the wild-type RPE65 gene were injected subretinally [1]. Excitingly, each of the three patients demonstrated improvements in retinal function, as measured on a variety of tests. Patients in this study were aged between 19 and 26 years, an age when most of the photoreceptors have already been lost to the disease; therefore, the potential functional recovery obtained is of great importance. Moreover, there were no severe apparent local or systemic adverse events elicited by the AAV2 vectors [1].

In the same issue of *New England Journal of Medicine* (May 22, 2008), Bainbridge *et al* reported data from a sister trial conducted in parallel at the Institute of Ophthalmology, University College London, UK [2]. Three patients with mutations in the same gene as those treated in the US were treated with a similar AAV2 vector expressing a normal version of RPE65 under the control of its endogenous promoter. The promoter controlling expression of RPE65 apparently being the only significant difference in the gene therapy vectors used at both institutions. Patients treated in London were aged between 17 and 23 years and, although some subjective responses were improved, no objective responses were observed. As in the US study, no evidence of serious local or systemic side effects were detected, although patients in the UK were treated with perioperative systemic corticosteroids [2].

Added to three more patients from a second US clinical trial [3], these trials are highly significant in that a total of nine patients affected by inherited and untreatable retinal degeneration underwent gene therapy treatments without adverse events and with potentially

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significant improvements in vision. It is also important that the age of patients treated at all three centers appear to have been included in the clinical trials based on their capacity to provide written informed consent. This differs from the treatment of boys with SCID-X1, all of whom were treated with gene therapy as boys or even babies with consent provided by their parents or legal guardians.

In the case of SCID-X1, there is no effective treatment available and eventually all affected boys will die from a fatal infection. Patients with LCA, however, will not die, but become totally blind sometime in their late teens to early twenties. For patients with SCID-X1, if bone marrow transplants are unavailable, treatments such as gene therapy are their only chance of survival; thus consent is required as children, that is from their parents or legal guardians. Conversely, LCA causes a progressive loss of photoreceptors and destruction of the retina, but does not cause death. A normal copy of RPE65 is required for photoreceptor function and photoreceptors containing a mutated version of this gene will die, resulting in retinal degeneration. Although a normal copy of the RPE65 gene can be transferred into the retina, if photoreceptors are missing, gene therapy will be too late to save the individuals' sight. Therefore, for patients with LCA, as the disease does not kill them, gene therapy treatment is not initiated until they are old enough to give consent. It appears, therefore, that it is ethically acceptable (at least for the early clinical trials) that this disease is allowed to progress to almost complete blindness before consent is gained for new experimental treatments.

In an ideal world, patients with LCA would be treated as children. At a younger age gene therapy would prevent ongoing photoreceptor death, and therefore potentially cure this disease and prevent the development of complete blindness. The ethical argument is likely to consider blindness prevention as a 'quality-of-life' rather than a 'life or death' issue. In postponing treatment until patients are old enough to consent, patients become eligible to participate in a clinical trial in which the chances of preserving their own visual function are significantly reduced, while still exposing them to potential adverse events. Currently, younger patients are not able to give consent, although gene therapy would have a greater chance of being truly effective if administered before total photoreceptor loss. Is this ethical reasoning sound, or should parents of such patients be given a choice to consent for their children? Although too young to consent themselves, consent to gene therapy would carry a much higher chance of successful treatment; the worst outcome of treatment failure of LCA would be blindness, the natural outcome of this disease.

Parents continue to provide consent to treatments for children too young to consent. For example, consent is provided for surgical manipulations, including: circumcision, which although religiously motivated constitutes an irreversible change in bodily structure; preventive vaccinations; and surgeries and chemotherapies for various cancers which, while preserving life, sometimes render children permanently sterile. As more and more gene therapies for untreatable inherited diseases move into the clinic, this question will arise again and again. A discussion of the ethics of consent should be initiated so that these arguments can be discussed in a transparent, fair and balanced manner to avoid any single profession having the final decision on where the ethical boundaries to be accepted by society are placed. Otherwise, the risk is that the success of novel therapies, such as gene therapy, will be held hostage to rather narrow interpretations of consent.

Another novel gene therapy clinical trial described the treatment of Parkinson's disease with AAV2 vectors that expressed glutamic acid decarboxylase [4,7]; these vectors were introduced into excitatory neurons of the subthalamic nucleus to make increased amounts of the inhibitory neurotransmitter GABA, and thus potentially reduce the symptoms of Parkinson's disease. Despite initial proposals to treat patients bilaterally, for safety reasons this clinical trial involved the unilateral treatment of patients. An interesting outcome of this design was that a comparison

could be made between treated and untreated sides of the brain. Data from this study suggested unilateral improvements. In addition, Eberling *et al* [8] and Marks *et al* [9] utilized AAV2 vectors that expressed either human aromatic acid decarboxylase or neurturin, respectively, in early phase clinical trials of Parkinson's disease. Eberling *et al* showed an increase in dopaminergic activity in patients with Parkinson's disease [8], while Marks *et al* [9] demonstrated acceptable safety and tolerability, absence of severe side effects and potential clinical improvements in the disease. In the absence of large numbers of treated patients and their respective controls, claims of clinical efficacy must wait until data are obtained from larger phase II and III clinical trials.

What ethical concerns do the Parkinson's clinical trials have in common with the clinical trial for LCA? Both had serious ethical issues to consider. In the case of the LCA clinical trial investigators had to select patients who were old enough to consent, while the Parkinson's disease clinical trials included patients with advanced disease that had already been treated by conventional standards of care, but had progressed nevertheless.

What pathophysiological aspects do both clinical trials share? Successful treatment of LCA by gene therapy is dependent on the number of surviving photoreceptors at the time of treatment; successful treatment of Parkinson's disease is dependent on the number of surviving nigrostriatal neurons at the time of treatment. Once photoreceptors or nigrostriatal neurons are dead, only cell replacement therapies would be effective.

Which patients have a better chance of successful treatment by gene therapy [10]? Presumably, younger patients with LCA and patients with Parkinson's disease who are at the initial stages of their disease. However, none of these patient populations have had the opportunity to be treated because of ethical concerns with age of consent, whether treatment preserves life or quality-of-life, and whether all other treatments available have already been tried and have failed. Ethicists, clinicians and scientists actively engaged in gene therapy agree that the ethics of gene therapy need to be reconsidered and re-evaluated [11-14].

The ethical principles used in these clinical trials may have been sound when considered in isolation, but the price paid is a delay in initiating treatment of those patient populations who could best benefit from gene therapy. It is time that disease pathophysiology and the potential benefit of treatment are considered in ethical decisions, and those patients and their parents and legal guardians are made aware of the ethical nuances related to novel experimental medical therapeutics and how these interact with the characteristics of individual diseases. Adhering rigidly to the currently accepted age of consent, waiting for the predictable failure of currently recognized standards-of-care, and simple interpretations of 'life' versus 'quality-of-life' issues, will continue to slow down and unnecessarily lengthen the already long and winding road imposed on novel medical experimental therapeutics, such as gene therapy. The time is right for a re-evaluation of the ethical principles used in the selection of patients as candidates for novel medical therapeutics, the success of which is intimately linked to individual disease pathophysiology.

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