

# Molecular Therapy

## A Call for Physiopathological Ethics

2008 has been a good year for gene therapy. Phase I clinical trials of gene therapy for the treatment of Leber's congenital amaurosis, Parkinson's disease, and others were published, and trials for brain, breast, head and neck, prostate, and ovarian cancers, among others, have made progress. Moreover, no additional cases of leukemia, beyond those reported so far, have been detected in the boys treated for X-linked severe combined immune deficiency (SCID-X1).

As described in a recent editorial in these pages,<sup>1</sup> gene therapy for inherited diseases received a boost (and positive press) with publications describing gene therapy for Leber's congenital amaurosis in nine young adults. In this disease, caused by mutation of the *RPE65* gene, retinal photoreceptors degenerate, leading to the progressive replacement of the retina by scar tissue. Patients usually go blind sometime in their mid- to late teens. No treatment to prevent, delay, or cure the blindness in these patients is currently available. In the first of three studies,<sup>2</sup> three patients were subretinally injected with an adeno-associated virus type 2 (AAV2) vector carrying a normal *RPE65* complementary DNA. The patients' ages ranged from 19 to 26 years, ages by which most of the photoreceptors have already been lost. Nevertheless, each of the treated patients showed improvements in retinal function. Moreover, there were no severe local or systemic adverse events.

A second study<sup>3</sup> also involved three patients, from 17 to 23 years old, with mutations in the same gene. They were treated with a similar AAV2 vector expressing *RPE65* under the control of its endogenous promoter. Although there was some subjective evidence of improvement, no objective responses were obtained. As with the first study, no serious local or systemic side effects were detected. A third study describing comparable outcomes was recently reported online.<sup>4</sup> Thus, a total of nine patients affected by an inherited, untreatable retinal degeneration have now shown potential improvements in vision in response to gene therapy, apparently without serious adverse events.

Another recent trial<sup>5,6</sup> described the treatment of Parkinson's disease patients with AAV2 vectors expressing glutamic acid decarboxylase to direct excitatory neurons of the subthalamic nucleus to

produce increased amounts of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid, with the aim of reducing the symptoms of the disease. The trial involved the unilateral treatment of patients, allowing researchers to provide data suggesting unilateral improvements in the function of treated Parkinson's patients' brain hemispheres. Two additional studies reported results of early-phase clinical trials of Parkinson's disease using AAV2 vectors expressing either human aromatic acid decarboxylase<sup>7</sup> or neurturin.<sup>8</sup> The findings indicated, respectively, an increase in dopaminergic activity in human patients<sup>5</sup> and acceptable safety and potential clinical improvements.<sup>6</sup> In the absence of large numbers of patients, controls, and placebo procedures, long-term claims of clinical efficacy will need to await larger randomized, double-blind, controlled phase II/III clinical trials.

At first inspection, the two sets of trials appear quite different. Leber's congenital amaurosis affects patients from birth, whereas Parkinson's mostly affects adults over 50 years of age. The older patients who were treated for Leber's had approximately less than 10% of visual acuity remaining at the time of treatment. Parkinson symptoms also appear when a large percentage of affected neurons has already been lost. The progressive neuron loss has important therapeutic implications for Parkinson's disease. In early Parkinson's, restitution of the synthesis of the neurotransmitter dopamine is effective. However, such therapy necessitates viable nigrostriatal dopaminergic neurons, and as they continue to die, the treatment loses efficacy. Thus, both sets of trials were performed on patients already missing a large percentage of either their target photoreceptors (Leber's) or nigrostriatal dopaminergic neurons (Parkinson's).

Given that the presence of either cell type is necessary for therapeutic efficacy, it would appear that neither set of trials was performed at a stage when patients could have derived maximum benefit from the gene therapy. In Parkinson's disease, patients currently must be treated by approved medications, and only after these have failed (and even more dopaminergic neurons have died) do patients become eligible for gene therapy. In Leber's congenital amaurosis, it is even more difficult to fathom why the trial was not performed in younger patients, who possess a much larger reserve of remaining live photoreceptors.

In patients suffering from SCID-X1, gene therapy was given to children after their parents had given informed consent. This did not appear to have been a possibility in the Leber's trials, in which the ethical argument might have considered blindness prevention a quality-of-life issue rather than a life-or-death issue, as for the SCID-X1 patients. Thus, the ethical opinion may have ruled to delay treatment of Leber's patients until they were able to consent to the treatment themselves, rather than allowing parents to provide such consent for the treatment of younger children. From an ideal therapeutic standpoint, however, gene therapy at an earlier age would have increased chances of success, because experimental studies indicate that gene replacement prevents ongoing photoreceptor death and disease progression to complete blindness. In such trials in older patients, while exposing subjects to identical potential adverse and side effects, the ethics applied restricted patients to consent to a treatment that has reduced chances of preserving their functional abilities.

Parents consent daily to procedures performed on children too young to consent to treatment. Parents consent to circumcision, preventive vaccinations, surgeries, and chemotherapies for various cancers that sometimes render children permanently sterile. As more and more gene therapies for the treatment of untreatable inherited diseases come to the clinic, the question of *at what age to treat* will continue to arise. Clearly we must open the ethical discussion so that these arguments can be reviewed in a transparent, fair, and balanced manner, without any particular profession being able to unilaterally determine the ethical boundaries applied to society at large.<sup>9</sup>

Similar concerns apply to consent issues in Parkinson's disease. To enter current clinical trials, patients need to fail existing treatments and progress to advanced disease, rather than enroll earlier when probabilities of success are likely to be higher. For both diseases, earlier treatment would expose patients to the same potential adverse side effects, but now their disease would be treated at a stage in which the likelihood of gene therapy's success would be significantly higher.

Importantly, the ethical discussion must take into account the physiopathological mechanisms of action of any novel molecular treatment such as gene therapy. Otherwise, the success of any new therapies will be held hostage to rather narrow interpretations of consent and risk-benefit analyses. A recent death in a clinical trial—most likely a side effect of high-dose sustained treatment with powerful immunosuppressants and a resultant systemic fungal infection rather than of the gene therapy—has thrown the gene therapy ethical world back into the limelight.<sup>10–13</sup> This could be

used as an opportunity for ethicists, clinicians, and scientists to again review and discuss the ethics of gene therapy.

The ethical principles applied so far are sound, and protection of patients from undue risk is our prime concern. However, the price we pay is very high when we withhold gene therapies from patient populations who could experience the greatest benefit. Patients, parents, legal guardians, and special patient representatives must be aware of the nuances of the ethics of novel experimental medical therapeutics and how these interact with the physiopathological characteristics of individual diseases, as discussed above. Rigid implementation of issues of “age of consent,” “failure of currently approved standards of care,” and “life versus quality of life” will continue to unnecessarily obstruct the already long and winding road for novel medical experimental therapeutics such as gene therapy. The time is ripe for a re-evaluation of the ethical principles used in the selection of patients as candidates for novel medical therapeutics, the success of which must be linked to individual disease physiopathology.

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