POLICY FORUM: MEDICAL ETHICS

Principles for Human Gene Therapy Studies

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The human gene therapy community finds itself struggling with technical and policy problems arising from several recently publicized adverse events in human gene therapy studies. The current discussion was catalyzed by the tragic death of Jesse Gelsinger, an 18-year-old patient with ornithine transcarbamylase (OTC) deficiency who died, apparently as a direct result of the experimental gene therapy studies being carried out by investigators at the University of Pennsylvania in Philadelphia and the National Children's Medical Center in Washington, DC.

Preliminary public review of the events leading to the tragedy in the Philadelphia OTC study was presented at a recent public meeting of the Recombinant DNA Advisory Committee (RAC) of the Office of Biotechnology Activities (OBA) of the National Institutes of Health. An ongoing Food and Drug Administration (FDA) investigation has already resulted in a compulsory hold of indefinite duration being placed on gene therapy studies at the Institute for Human Gene Therapy at the University of Pennsylvania and a voluntary hold on at least one other academic institution until possible deficiencies can be corrected. One commercially sponsored study was placed on temporary hold but now has been resumed. Additional inquiries by the involved universities, the Advisory Committee to the Director of the NIH, the United States Senate, and the executive branch are under way.

These events suggest that the gene therapy community has not fully succeeded in developing mechanisms to ensure the highest possible quality of clinical research. The intention of this discussion is to derive lessons from the preliminary information available and to reexamine the principles that constitute the foundation of clinical research in gene therapy.

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Human Experimentation Requires Careful Patient Selection and Protection

Human disease and therapy are, eventually, best studied in human subjects. Codes of medical ethics recognize the importance of appropriate human studies, as long as they rest on strong basic and preclinical science and voluntary informed consent by patients. To be truly "informed," a patient's consent must be based on current and complete information of the procedures and their potential risks and benefits.

The patient population with potentially the most to gain in the Philadelphia OTC study, patients with the neonatal lethal form of the disease, were justifiably included in the initial study design. However, investigators were advised by their institutional review board (IRB) and medical ethics consultants that phase I experiments (in which dose and safety are being tested) would be ethically unacceptable in these infants because of the danger of implying a potential benefit to desperate parents. The next-best study population was used instead—less severely affected older patients from whom informed consent and meaningful data might be more readily obtained. There is debate in the medical ethics community whether this decision to exclude desperately ill newborns was appropriate. The quandary of patient selection in this case underscores this general dilemma in medical ethics and the unrealistic degree to which we have come to expect therapeutic results in phase I studies.

Human Experimentation Involves Risks

Human experimental studies, genetic or otherwise, are "experimental" precisely because the results are not known beforehand. Preclinical studies sometimes indicate adverse outcomes that can be readily avoided. In other instances, adverse results are found, only in retrospect, to have been foreshadowed by clues during early testing that investigators were neither alert nor wise enough to appreciate. In still other studies, adverse outcomes could not have been predicted in animals and limited human trials. Preclinical studies did not predict the discovery that the diet medication fen-phen is associated with potentially life-threatening cardiac valvular damage. Likewise, the recent withdrawal from the market by the FDA of a rotavirus vaccine came only after large-scale human experience with the vaccine.

Adverse Results Do Not Invalidate the Rationale of Gene Therapy

Apparent "failures" in early phaseI/II or even phase III studies do not necessarily indicate a therapeutic wild-goose chase. Because gene therapy is highly experimental and many patients are desperately ill, serious adverse events and even deaths will occur. It is vital to understand the reasons for unexpected results or clinical failures to allow the development of corrected procedures and improved experimental methods. For example, problems with polio vaccines due to persistence of live disease-causing poliovirus in incompletely inactivated preparations and the presence of SV40 in the vaccine were identified early, corrected, and used to develop improved programs.

The development of gene therapy is similar to vaccine and drug development. Drug development is difficult and expensive, and gene therapy will not be simpler. The pharmaceutical industry, more mature and experienced than the gene therapy community, devotes enormous research and financial resources to studies of the biodistribution, pharmacological properties, stability, and metabolic properties of a potential new drug, as well as the physiological, immunological, and teratogenic effects on the host. Despite such care, because of the enormous complexity of human physiology and disease, and because even the most extensive animal data do not always faithfully predict responses in humans, adverse clinical responses have occurred and will again. The same understanding of pharmacokinetics and mechanisms has not been available for gene therapy trials. Some clinical applications have simply outstripped scientific understanding of the disease model or the properties of the vectors, resembling an army too far ahead of its supply lines. Despite clinical urgency, there is a need to develop a similar degree of rigor for gene transfer agents as for small molecule therapeutics or viral vaccines.

Despite the caveats regarding the need for better knowledge, the search for optimum methods should not paralyze attempts to use available tools to conduct clinical research studies. To make progress, one must accept the limitations of knowledge and simultaneously use available information to ease suffering and to continue research into improvements in technology.

Informed Consent Is Crucial to Patient Protection

The single most important mechanism for ensuring patient protection from inherent risks of clinical experiments, unrealistic ex-

pectations, and potential conflicts of interest of the investigator is accurate and full disclosure of potential risks and benefits and a well-executed informed consent process. For gene therapy studies, the FDA and RAC review the adequacy of locally approved informed consent procedures during the protocol approval process. The FDA concluded that there were deficiencies in the informed consent process in the OTC study that resulted in incomplete disclosure of all potential risks to the subjects or their families. Additional troublesome public revelations of potential lapses in quality control and in patient protection have been made for other gene therapy studies.

Exaggerated expectations and potential conflicts of interest of investigators pose additional problems to the informed consent process. In 1995, an NIH advisory committee chaired by Stuart Orkin and Arno Motulsky criticized the gene therapy community for its overly optimistic public portrayal of gene therapy experiments and for unsubstantiated claims for efficacy (*1*). There is still too ready a tendency by some in the gene therapy community to exaggerate potential benefits at the expense of full disclosure of potential risks. If that tendency is the result of optimism, it is at least unfortunate and should be guarded against. If it was determined that risks were intentionally omitted or misstated, appropriate sanctions by the gene therapy community and oversight bodies should be applied.

Dealing with Financial Conflict of Interest

The issue of conflicts of interest is magnified by the very large role that biotechnology and pharmaceutical industries have come to play in gene therapy. In many cases, academic investigators have had to forge commercial collaborations to implement clinical studies because of the high costs (production and testing of a gene vector usually exceeds several hundred thousand dollars). Although commercial interactions have facilitated clinical studies, they have also introduced corporate financial interests and investigator economic conflicts. Therefore, at minimum, involved investigators should disclose direct commercial ties in the informed consent process. Those investigators with direct financial interest in the study outcome should recuse themselves from patient selection, the informed consent process, and study direction.

Improvements Are Needed in Review and Regulation

During the early phase of clinical studies of human gene transfer, the RAC played a major role by providing an avenue for public evaluation of the scientific basis and patient protection aspects of a proposed study. The FDA shared responsibility for oversight of gene therapy studies through its traditional regulatory function of ensuring safety and efficacy. In 1997, in response to an advisory committee report to the NIH director, the FDA assumed the principal regulatory and oversight responsibility for gene therapy proposals, and the RAC was given the function of catalyzing public awareness and understanding of the issues of gene therapy. It also retained a secondary responsibility to determine whether studies submitted to the FDA utilized technological concepts and tools so novel that they required further public review.

An important difference between the RAC and FDA processes is that the RAC reviews of proposals and adverse-event reporting are public and open, whereas FDA is required by statute to carry out these functions privately and without provision for public disclosure. In a field as immature and filled with public interest and concern as gene therapy, more, rather than less, public review seems desirable. A cohesive mechanism must be developed in which primary regulatory control stays with the appropriate regulatory agency—the FDA—but which more effectively takes advantage of the advisory role of the RAC or a RAC-like body and also uses the RAC as a conduit for public discussion and disclosure before protocol approval. It is encouraging that discussions are under way between the RAC, FDA, and NIH through the Advisory Committee to the NIH director on potential mechanisms to provide this kind of process.

Gene Therapy Trials Require Improved Monitoring

For the field to progress, investigators must have more ready access to the clinical experience in other studies, and it is therefore particularly encouraging that the OBA has reaffirmed its intention to develop a gene therapy database that will make the occurrence and nature of adverse events available online to other gene therapy investigators (*2*). Such a database can only succeed if investigators report their adverse events, and disclosure is useful only if mechanisms exist to collate, evaluate, and promulgate such information.

The existence of widely different reporting requirements has contributed to uncertainty and, quite probably, to deficiencies in reporting. The FDA requires that serious, unexpected, or related events be reported to the agency within 7 days if there is a patient death, or within 15 days for other serious adverse events. All other events are to be included in annual reports (*3*). The words "serious," "unexpected," and "related" allow room for interpretation by investigators and study sponsors; the NIH requirements are less flexible. It is therefore possible, as the oversight agencies and several investigators have recently discovered, to be in compliance with the FDA requirements but not with the NIH guidelines. The NIH has recently proposed strengthening its reporting requirements through amendments of the NIH guidelines in which the definition of adverse events is clarified, and there is notification that such reports may not contain any confidential trade secrets or commercial and financial information (*4*). The NIH has also notified all federally supported institutions to review their policies and procedures to ensure that they are in compliance with reporting requirements (*5*). The FDA has stated that it will notify the RAC of the receipt of all adverse events in a gene therapy study (*6*).

Conclusions

Scientific and policy problems in gene therapy studies, together with the explosive growth of clinical studies, challenge the academic gene therapy community, commercial biotechnology and pharmaceutical firms, regulatory agencies, and professional societies such as the American Society of Human Gene Therapy to work together to improve current practices and infrastructures. Announcements of new initiatives for FDA and NIH that would require earlier review of researcher's plans for monitoring safety and quarterly meetings to promote communication are encouraging developments. Further critical steps toward that goal would include RAC determination of the need for full public evaluation of protocols before investigational new drug (IND) assignment by FDA and IRB approval; the development of a single, uniform mechanism for reporting adverse events to the RAC, FDA, and other relevant agencies; establishment by OBA of its proposed public database of all adverse events; and nonparticipation of investigators with financial interests in study outcomes in patient selection, the informed consent process, and direct management of clinical studies. While there is need for improvements, there is also much to celebrate—major technical advances that promise imminent proof that the lives of patients can eventually be made better by gene therapy.

References and Notes

1. S. Orkin and A. Motulsky, www.nih.gov/news/panelrep.html, 7 December 1995.
2. Testimony of A. Patterson, www4.od.nih.gov/oba/patterson2-00.pdf, 2 February 2000.
3. FDA Manual of Regulatory Standard Operating Procedures and Policies, www.fda.gov/cber/regsopp/91101.htm; www.fda.gov/cber/regsopp/91102.htm; and www.fda.gov/cber/ind/21cfr312.pdf.
4. Minutes of RAC meeting, 5 September 1999, www4.od.nih.gov/oba/9%2D99pro.htm.
5. Letter from A. Patterson to federally funded institutions, 22 November 1999.
6. Letter from K. Zoon to Investigational New Drug Sponsors and Principal Investigators, www.fda.gov/cber/ltr/gt110599.htm, 5 November 1999.