Ethical aspects of clinical trials in gene therapy

S K Pandya

On September 14, 1990, researchers at the U.S. National Institutes of Health performed the first approved gene therapy procedure on four-year old Ashanti DeSilva, born with severe combined immune deficiency. Doctors removed her white blood cells, let the cells grow in the lab, inserted the missing gene into the cells, and then infused the genetically modified blood cells back into the patient's bloodstream. Laboratory tests have shown that the therapy strengthened Ashanti's immune system. She no longer has recurrent colds, and has been allowed to attend school.

This simplified explanation of a gene therapy procedure is little more than an optimistic first chapter in a long story; the road to the first approved gene therapy procedure was rocky and fraught with controversy. The biology of human gene therapy is very complex, and there are many techniques that still need to be developed and diseases that need to be understood more fully before gene therapy can be used appropriately. The public policy debate surrounding the possible use of genetically engineered material in human participants has been equally complex.

'Somatic' and 'germ line' therapy

Insertion, correction or deletion of genes can be carried out in 'somatic' (body) cells that are well differentiated and play no role in reproduction of the species or in 'germ line' cells, which are concerned with reproduction.

Since the germ cells carry the genes that will be passed on to the next generation, there has been strong opposition to any form of genetic manipulation in them, no matter how well intentioned because of unforeseeable effects on future generations. Others have argued that with proper regulation and safeguards, germ-line gene therapy is a logical extension of the progress made to date, and an ethically acceptable procedure.

Sunil K. Pandya,, *Flat 11, fifth floor, Shanti Kutir, Marine Drive, Mumbai 400 020. E-mail:* shunil@vsnl.com

Techniques

The first somatic cell gene therapy procedure inserted a normal gene into the DNA of cells in order to compensate for the non-functioning defective gene. This technique involves obtaining blood cells from a person afflicted with a genetic disease and then introducing a normal gene into the defective cell. The normal gene is delivered using a domesticated retrovirus that infects the cell, introducing the properly functioning gene. Retroviruses can infect many types of cells, so it is important to develop gene transfer techniques that allow only retroviruses to deliver genes to a cell and then remain there. Furthermore, the new gene must not get to the wrong place in the genome of the cell.

For cystic fibrosis, another kind of virus called an adenovirus has been used as the vector for the new gene. In still other studies, the new DNA is introduced directly into skin cells or even tumor cells.

Germ-line gene therapy is technically more difficult, and as noted, raises more ethical challenges. The two main methods of performing germ-line gene therapy would be: 1) to treat a pre-embryo that carries a serious genetic defect before implantation in the mother (using in vitro fertilisation techniques); or 2) to treat the germ cells (sperm or egg cells) of afflicted adults so that their genetic defects would not be passed on to their offspring. This approach requires the technical expertise to delete the defective gene and insert a properly functioning replacement.

The following criteria must be met for selecting diseases for gene therapy: the disease is incurable and life-threatening; the organ, tissue and cell types affected by the disease have been identified; the normal counterpart of the defective gene has been isolated and cloned; the normal gene can be introduced into a substantial sub-fraction of the cells from the affected tissue (and introduction of the gene into the available target tissue, such as bone marrow, will somehow alter the disease process in the tissue affected by the disease); the gene will direct the production of enough normal protein to make a difference, and, finally, techniques are available to verify the safety of the procedure.

Arguments for and against

The central argument in favour of gene therapy is that it can be used to treat desperately ill patients, or to prevent the onset of serious illnesses. Conventional treatment has failed for the candidate diseases for gene therapy, and for these patients, gene therapy is the only hope for a future. Many commentators liken somatic cell gene therapy to other new medical technologies, and argue that we have an obligation to treat patients if we can.

Concerns about somatic cell gene therapy include the slippery slope argument. Is it possible to distinguish between 'good' and 'bad' uses of the gene modification techniques? Should the potential for harmful abuse of the technology keep us from developing more techniques?

Other commentators have pointed to the difficulty of following up with patients in long-term clinical research. Gene therapy patients would need to be under surveillance for decades to monitor long-term effects of the therapy on future generations. Some are troubled that many gene therapy candidates are children too young to understand the ramifications of gene therapy treatment.

Others have pointed to potential conflict of interest problems pitting an individual's reproductive liberties and privacy interests against the interests of insurance companies, or society not to bear the financial burden of caring for a child with serious genetic defects. Issues of justice and resource allocation have also been raised: can an overburdened health care system afford such expensive therapy? Who should receive gene therapy? Is it to be made available only to those who can afford it?

Arguments specifically against the development of germ-line gene therapy techniques include:

- They involve too much scientific uncertainty and the long-term effects are unknown.
- They would open the door to attempts at altering traits not associated with disease, exacerbating problems of social discrimination.
- They involve research on early embryos and affect their offspring, creating generations of research participants who cannot offer consent.
- They will never be cost effective enough to merit high social priority;
- They would violate the rights of subsequent generations to inherit a genetic endowment that has not been intentionally modified.

How gene therapy can go wrong

Eighteen-year-old Jesse Gelsinger, a participant in the experimental gene therapy trial for ornithine transcarbamylase deficiency, died on Friday, September 17, 1999, four days after being injected with a high-dose viral vector and therapeutic gene at the University of Pennsylvania. Findings suggest that the experimental drug used in the trial – a modified cold virus, or vector, incorporating a potentially corrective gene for Mr. Gelsinger's genetic disease – initiated an unusual immune-system response that led to multiple organ failure and death. He was the first person known to have died as a result of gene therapy.

Subsequent investigations revealed that the deaths of six gene therapy patients had not received public disclosure. Gelsinger's death also raised questions about researcher entrepreneurial activities and conflict of interest, and about government oversight procedures.

Misplaced research ethics

Journalists have traced what began as a mystery and is emerging as a tale of botched oversight and misplaced research ethics. The Pennsylvania trial and its fallout have cast a long shadow on this mostly unproven field, and raised questions in the public's mind about its safety and the protection of participants.

Jesse and his family may not have been advised of the risks inherent in his trial, including information concerning the deaths of primates. Jesse and other patients thus may not have given informed consent. Jesse had high ammonia levels which made him ineligible to be included the trial. Inherent conflicts of interest may exist concerning the ability of researchers and biotech companies to protect their own financial interests and at the same time protect patients from undue risk.

Boston University's leading medical ethicist, George Annas, pointed out that many of the trials are unlikely to be stopped voluntarily because of the involvement of publicly traded biotech firms. "A lot of these companies may have too much at stake," he said. "They may think it's wrong for their stockholders. But that reveals a major problem we have. When researchers worry more about share values than about patients, we're in trouble." The lion's share of adverse effects in gene therapy trials have not been reported to the public oversight body, the Recombinant DNA Advisory Committee (RAC). On 1 February 2000, *BBC* reported: "Hundreds of failed gene therapy experiments, including a number of deaths, have been revealed in the US. The US National Institutes of Health (NIH) has confirmed that only 39 of the 691 'serious adverse events' now logged had been reported to them 'immediately', as required by federal regulations."

Some patient deaths in gene therapy trials may have been wrongly ascribed to underlying diseases rather than the treatment itself.

Subsequent American actions

After months of governmental and internal review, the University of Pennsylvania discontinued gene therapy trials on humans. Massachusetts General Hospital voluntarily suspended its own gene transfer trials. Even before that, a gene therapy trial being conducted on cancer patients at Boston's Beth Israel Deaconess Medical Center was voluntarily suspended. Early this year, the US FDA shut down clinical trials at two eminent research institutions, Duke University and the University of Alabama at Birmingham. The National Academy of Sciences' proposal that medical errors be made available to the public was vetoed by federal health officials.

The state of oversight of all clinical trials and medical mistakes is, and has been for some time, in crisis even in the USA. Recently uncovered problems with gene therapy trials are part of a larger picture of problems with human clinical research and the protection of research participants. In 1998, the Health and Human Services' Office of the Inspector General issued a report stating that the oversight regarding informed consent and lapses of all multicentre clinical trials is woefully inadequate due to their size, decentralisation, and the increasing funding of research by private sources; the office called for reform at the local institutional review board (IRB) level.

Reporting lapses brought to light in gene therapy trials should not be surprising given reports of such failures in other clinical research. For years, the media has reported shocking lapses in protocol, oversight, reports of adverse events, and judgment of some clinical investigators at a wide range of top academic institutions.

On 24 May, 2000, *The New York Times* reported the decision by the Clinton administration to levy fines of up to $250,000 on scientists who violate federal rules for human research and $1 million on the universities that employ them for violations of human research rules.

The government will require bioethics training for clinical researchers and will lay down clear conflict-of-interest guidelines for doctors who have financial stakes in their studies. There will be new requirements for monitoring small clinical experiments, which are not subjected to the same intense regulatory scrutiny as larger studies. Research institutions will now be required to audit records for proof that patients have truly given their 'informed consent' to participate.

Lessons learnt in the US

Experts reviewing the death of Jesse

Gelsinger concluded that the institute was not capable of complying with the federal regulations governing clinical trials. Should clinical trials continue under the institute's auspices, the report said, "hundreds of standard operating procedures must be developed, recorded and put into exact operation."

Some of the steps initiated at the University of Pennsylvania:

- Assessing all clinical trials to determine the level of monitoring necessary for compliance with regulations.
- Initiating a comprehensive review of ethical decision-making in human research, and creating an Institutional Review Board (IRB) with special expertise in evaluating gene therapy.
- Conducting a formal, comprehensive review of the IRB system.
- Implementing a new database tracking system that identifies primary and secondary reviewers and monitors IRB discussion of substantive issues and its recommendations for changes in protocols and consent forms.
- A new 24-hour adverse event hotline.
- Substantial, regular training and education for IRB members and staff.
- Training for School of Medicine faculty, which ultimately will be integrated into a requirement for certification of both principal investigators and research coordinators before permitting submission of protocols for IRB review.
- Developing new standard operating procedures for IRB members that delineate the need for continuing review and the responsibilities of the convened IRB, the chair and the staff.
- Reviewing policies and procedures on conflicts of interest, including those inherent in investment and funding of provocative medical therapies.
- Review of clinical trials without external sponsorship and monitoring by a professional contract research firm to determine the need for additional monitoring.
- Developing a set of standards to guide the review and monitoring of all clinical trials.
- Developing a compendium of Standard Operating Procedures for research involving human subjects and a process for ensuring that all investigators have access to, are cognisant of and in full compliance with these procedures.
- The School of Medicine will establish a new, free-standing Department of Bioethics that will include the current Center for Bioethics.

In March 2000, the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) announced initiatives to further strengthen the safeguards for individuals enrolled in clinical studies for gene therapy. The FDA requires all sponsors of gene therapy trials to supply additional information about cell banks, viral banks and other gene therapy products produced or generated in their facilities for potential use in non-clinical or clinical studies of human gene therapy. Among other gene therapy related information, the FDA is asking the sponsors to provide quality control information for each lot of products produced in their facilities or used in their clinical trials.

Clinical trial monitoring is a powerful tool for the protection of research subjects during a trial. Monitors selected by to the sponsor or the sponsor's designee verify that the rights and well-being of human subjects are protected; that the conduct of the trial is in accordance with the protocol, regulatory requirements, and good clinical practices; and that data reporting (including safety reporting to IRBs, the FDA, and the NIH) is accurate and complete.

Sponsors of gene therapy trials are now routinely required to submit their monitoring plans to the FDA which will review these monitoring plans and seek modifications as warranted to improve the quality of monitoring. The FDA will also perform surveillance and 'for cause' inspections of clinical trials to assess whether the plans are being followed and whether monitoring has been adequate to identify and correct critical problems. The sponsors will also have to address such issues as the experience and training of the monitors and the adequacy of the monitoring in their plans.

Harnessing genetic research for good will require guidelines, inter-disciplinary dialogue with people from all religions, from all scientific disciplines, as well as politicians.

Current Indian policy on research in gene therapy

The draft document on *Ethical guidelines on biomedical research involving human subjects* produced this year by the Indian Council of Medical Research restricts studies to somatic cell gene therapy. Such studies are permitted only for the purpose of preventing or treating serious disease. Germ line therapy is prohibited at present.

Questions for India

Are we anywhere near America in consciousness on medical ethics, ensuring the rights of citizens or the enforcement of laws? If not, we need to be even more acutely conscious of the many pitfalls in clinical research on gene therapy. In the absence of an authoritative agency that can create and enforce guidelines, the responsibilities on the clinical researchers in this field will be daunting.

Second, are our researchers blessed with the qualities that will enable them to stand up to the powerful financial giants that play in this field in the hope of obtaining data cheaply from countries such as ours so that they can add further billions of dollars to their already massive holdings?

This essay is an extract of a presentation made by Dr Pandya at the Cancer Research Institute, Mumbai.

Some suggested reading:

1. Shalala D: Protecting research subjects — what must be done. *N Engl J Med* 2000; 343 (11).

2. Report on university protections of human beings who are the subjects of research. Washington, D.C.: Association of American Universities, 2000.

3. Recruiting human subjects: pressures in industry-sponsored clinical research. Washington, D.C.: Department of Health and Human Services, 2000.

4. Henney JE. Remarks. Presented at the Association of American Medical Colleges Council of Teaching Hospitals Spring Meeting, Washington, D.C., May 10-12, 2000.

5. Institutional review boards: their role in reviewing approved research. Washington, D.C.: Department of Health and Human Services, 1998.

6. Angell M: Is academic medicine for sale? *N Engl J Med* 2000; 343: 1516-19.

7. ICMR: Draft consultative document on