REGULATION

GENE THERAPY NEARING U.S. CLINICAL TRIALS

WASHINGTON, D.C.—Researchers are carefully preparing for the first clinical tests of gene-replacement therapy, with the earliest efforts on seriously ill young patients probably to be formally reviewed this spring. The two federal agencies that are overseeing emerging plans for such experiments, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), went through a “dry run” review of such a proposal late last year. Specifically, officials and committee members considered whether the “compassionate use” of unproven experimental procedures can justify trials in desperate medical cases.

FDA has authority to review all research involving the use of drugs and related products in humans. Besides an interest in safety and efficacy of gene-therapy procedures, FDA will scrutinize materials to see whether they can be produced reliably from one trial to another.

Within NIH, the Recombinant DNA Advisory Committee (NIH-RAC) and its human gene therapy subcommittee are providing a forum for public discussions of the new technology—developing general guidelines and promising to review proposals in the same spirit that RAC evaluated early gene-splicing experiments. The committee has also adopted a “Points to Consider” document, which includes discussions of ethical as well as scientific issues.

At a meeting last December, the NIHRAC subcommittee evaluated a lengthy preclinical data document, which was prepared by W. French Anderson of NIH and his collaborators at NIH and Memorial Sloan Kettering Cancer Center (New York, NY). These researchers are planning a gene-therapy procedure to correct a rare hereditary disease that results from a deficiency of the catabolic enzyme adenosine deaminase (ADA). This genetic defect leads to a form of severe combined immune deficiency (SCID) disease, whose victims usually do not survive the first two years of life.

The preclinical data document, altogether several hundred pages in length, candidly outlines current gaps in scientific knowledge. Some of these can be closed only by conducting limited clinical trials.

The NIH group and outside reviewers identify three major scientific problems:

- Only low and unsustained levels of ADA activity have been measured

in animals into which human ADA genes have been introduced experimentally;

- An alternative and perhaps safer enzyme-replacement therapy is under intense development; and

- The risks from contaminating helper viruses used as part of the gene-therapy procedure are difficult to evaluate.

Gene therapy to correct ADA deficiency must be judged against two principal alternative therapies: bone marrow transplantation (BMT) and, more recently, enzyme replacement therapy with protein that is conjugated to polyethylene glycol (PEG).

Although BMT can be highly effective, immunologically matched healthy donors (usually siblings of the patient) are available for only about one-third of the patients. When close

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matches are not possible, drug treatments and irradiation may be used to improve the likelihood of a successful graft, but such procedures further increase the risks for the recipient.

Meanwhile, direct enzyme replacement therapy has not yet proved clinically successful, but a new approach involving PEG-conjugated ADA appears more workable than its predecessors. Only a few clinical cases have been reported so far, and the immune systems of the patients have been slow to show sought-after activity, according to both Anderson and Robert Parkman, who is from the Children’s Hospital of Los Angeles.

The proposed gene-therapy trial’s third major scientific problem revolves around the vectors being used to move the replacement ADA gene from one cell type to another—ultimately, into stem cells of young SCID patients. Because most of the viral genes have been removed from the vector, which is derived from the Moloney murine leukemia retrovirus, a helper virus must be used during some stages before the materials are introduced into patients. Thus, concerns focus on whether the remaining genes of the retrovirus can do any significant harm and on how much contaminating helper virus may be carried along. Nothing yet indicates that exposure to the vector system

presents acute or chronic risks—either for recipient patients or for other individuals in contact with them—but such negative evidence cannot be considered conclusive.

Despite these uncertainties, Anderson and his colleagues last autumn overcame some of their hesitancy about a clinical trial. Until that time, their concerns about raising “false hopes” kept them from submitting “a protocol that could not ethically be carried out.” Now, they say, “it would be appropriate to prepare a limited clinical protocol [that] meets the minimum requirements for efficacy and safety for a ‘last-hope’ procedure.”

The NIHRAC subcommittee’s response to this change in attitude was mixed. At first, members of the panel seemed unsettled by what appeared to be a major change in approach by Anderson and his colleagues. However, the panel eventually came to view the research group’s altered stance as a change in emphasis rather than something more fundamental.

“What will you learn?” asks Richard Mulligan, a consultant to the NIH panel who hails from the Whitehead Institute for Biomedical Research (Cambridge, MA). “If you did two patients and there was no effect, would you do more?”

Anderson admits there are no simple answers to such questions. He points out, however, that gene-transplant experiments in monkeys were suspended two years ago when they failed to show a positive effect. “But now we have new things to try,” he adds.

Earlier, gene therapy was “being looked at as a first-line alternative,” notes Parkman. “Now we’re moving to look at patients who have failed other therapies.” Although there is “a danger of exploiting the last-hope category,” says panelist Alexander Capron from The Law Center at the University of Southern California (Los Angeles), it also is “within our [Points to Consider] document to ask researchers to look only at a patient subgroup. I don’t see it as shifting gears.”

“There is a long history of human therapies and products that seemed dubious at first,” stresses panel member Henry Miller from FDA. And even if such an experiment in desperate patients is accompanied by an “irreducible risk,” adds Capron, this kind of trial could bring benefit to others if it is “designed to provide useful information.”

—Jeffrey L. Fox