



GENE THERAPY

Second Child in French Trial Is Found to Have Leukemia

For the second time in 4 months, a child has developed a leukemia-like disease after receiving gene therapy at the Necker Hospital for Sick Children in Paris. Concerned about the safety of such trials, the panel that monitors U.S. research in the field scheduled a public meeting this week to review the clinical data and weigh its next steps.

The news of a second case of cancer in the French trial reached the U.S. Food and Drug Administration (FDA) on 20 December and quickly spread to other gene-therapy researchers. FDA responded by putting a “clinical hold” on U.S. studies that, like the French trial, use retroviruses to shuttle therapeutic

disorder called X-linked severe combined immunodeficiency (X-SCID) had developed a blood problem. A type of immune cell—a $\gamma\delta$ T cell—whose growth had been boosted by gene therapy was discovered to be replicating at an unhealthy rate. French clinicians treated it as though it were leukemia and reported within several weeks that they had successfully stopped its proliferation. But Fischer himself raised the possibility that his X-SCID cure—which is credited as the first unequivocal success for gene therapy—could have caused the cancerlike response.

FDA ordered a pause in all three U.S. clinical trials using retroviruses. The only

with closer monitoring (*Science*, 18 October 2002, p. 510). But none actually resumed.

The second adverse event in the Necker trial could have a devastating impact on researchers’ plans and the hopes of patients who volunteered for these trials. “It kind of threw a wet blanket over everything,” said Joseph Glorioso, president of the American Society of Gene Therapy and a molecular biologist at the University of Pittsburgh. “We will have to take a hard look” at possible causes, he says, including the chance that selectively promoting the growth of certain target cells in blood—as this type of gene therapy aims to do—could increase the likelihood of cancer.

Nobody knows how great the risks to patients are, admits Brian Sorrentino, leader of a gene-therapy group based at St. Jude Children’s Research Hospital in Memphis, Tennessee, which treats a type of immune deficiency similar to X-SCID called JAK-3. “I don’t think we can use any of the prior data” to develop risk estimates, he says, because clinicians may not have focused on the relevant parameters. In October, the risk of cancer in X-SCID therapy looked to be no higher than 1 in 10, he says, but now it could be 2 in 10. The new odds “raise a real red flag,” says Glorioso.

Jennifer Puck, who leads a gene-therapy group at NIH’s National Human Genome Research Institute that is targeting X-SCID, suggests that the age of patients in gene-therapy trials may be important. She notes that both of those who experienced adverse events in Fischer’s trial were younger than 3 months when they received therapy.

U.S. health officials and researchers are scrambling to assess the news, says Philip Noguchi, FDA’s leading gene-therapy expert. “We’re trying to learn whether this is a coincidence or something similar to the first case,” in which the retrovirus inserted itself into a gene that’s known to promote cancer. “Those data are coalescing to make it look similar: The therapy that clearly works may also be responsible for adverse events.”

If that’s true, says Noguchi, patients may face a “poignant dilemma” that offers them the chance of better health through an experimental gene therapy at the risk of contracting leukemia. FDA’s Biological Response Modifiers Advisory Committee will discuss the policy implications at its next meeting on 28 February.

—ELIOT MARSHALL

With reporting by Jocelyn Kaiser.

Gene Therapy Studies Under Review

Lead investigator	Institution	Disease	Status
A. Fischer	Necker Hospital, Paris	X-SCID	on hold
H. Malech and J. Puck	NIH	X-SCID	on hold
B. Sorrentino and R. Buckley	St. Jude Children’s, Memphis; Duke	JAK-3 deficiency	on hold
A. Thrasher	Inst. of Child Health, London	X-SCID	on hold
K. Weinberg and D. Kohn	NIH and Children’s Hospital, LA	X-SCID	on hold
F. Condotti and D. Kohn	NIH and Children’s Hospital, LA	ADA-SCID	on hold
C. Bordignon	San Raffaele Institute, Milan	ADA-SCID	on hold

genes into the chromosomes of target cells; most were already on pause for a safety review (see table). Meanwhile, the Necker Hospital’s lead investigator, Alain Fischer, asked colleagues around the world to keep the information confidential until after he had spoken with the families of the 10 children in the experiment. At press time, Fischer had not gone public and declined to discuss the details. He said that he intended to present his data on 17 January to the Recombinant DNA Advisory Committee (RAC) of the U.S. National Institutes of Health (NIH).

This adverse event, according to researchers in the field, mimics another one that came to light in September (*Science*, 4 October 2002, p. 34). In that case, Fischer told health authorities in France and abroad that one of 10 boys treated by his group for a

trial of this type not to pause for review was one run by Adrian Thrasher at the Institute of Child Health in London. It suspended therapy this week.

When the first adverse event appeared last fall, FDA and RAC sought outside advice on whether to suspend similar trials in the United States or to impose new reporting requirements. Some experts warned officials not to overreact, saying that the cancer might have been triggered by a harmful genetic mutation not related to the therapy. They noted that two other people in the child’s family also had developed cancer at an early age. Others, however, felt that the clinical data strongly suggested that the gene therapy itself had triggered the dangerous T cell proliferation. In the end, U.S. authorities decided to allow the potentially risky trials to continue,