



Injury to Research Volunteers — The Clinical-Research Nightmare

Alastair J.J. Wood, M.D., and Janet Darbyshire, M.B., Ch.B.

At 8 a.m. on Monday, March 13, 2006, eight healthy young men entered a trial of a drug under development by the small German immunotherapeutics company TeGenero. Six of the volun-

teers were assigned to receive active drug, and two were to receive placebo. The trial was being conducted for TeGenero by Parexel, a large contract research organization, at its facility at Northwick Park Hospital outside London. The six volunteers were to be the first humans to receive TGN1412, a humanized monoclonal antibody designed as an agonist of the CD28 receptor on T lymphocytes, which stimulates the production and activation of T lymphocytes. It was hoped that this product would benefit patients with B-cell chronic lymphocytic leukemia or autoimmune diseases such as multiple sclerosis or rheumatoid arthritis. Preclinical testing, including tests

in rabbits and monkeys that used doses up to 500 times as high as the doses received by the first group of volunteers,¹ reportedly showed no signs of toxicity.

However, after receiving injections of TGN1412, the six volunteers became desperately ill, had multiple-organ failure, and were transferred to an intensive care unit² with what has been described as a cytokine release syndrome.¹ As of April 5, five of the volunteers had been discharged from the hospital, and the other man appeared to be recovering.² This unexpected and devastating outcome is currently under investigation by the relevant authorities under the supervision of the United

Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), which originally approved the trial and its protocol. A preliminary report has now been completed and released.¹ The serious injuries to these volunteers compel us to reassess the safety of such clinical trials in general, particularly those involving healthy volunteers.

At some point in the development of every drug, the drug must be given for the first time to humans in a phase 1 trial. Until now, such trials have had a remarkably good safety record,³ reflecting both the extent of the preclinical and animal testing that precedes them and the safeguards built into their own designs. In particular, it is standard practice to begin with very small doses, often orders of magnitude below those determined to be nontoxic in animals and those expected

to produce any effect in humans. Doses are then increased slowly, as the experience at lower doses is continually evaluated. Life-threatening toxic effects in a phase 1 trial, such as those seen in the TeGenero study, are virtually unheard of, although the tragic death of Jesse Gelsinger in a gene-therapy trial at the University of Pennsylvania in 1999 certainly highlighted the potential for harm.⁴ Why have most trials been free of such incidents, and what can we do to enhance their safety even further?

System or human failures — such as errors in dosage, manufacturing, or administration — are usually prevented by rigorous procedures for drug preparation and administration. According to the MHRA's preliminary investigation, such errors do not appear to explain the life-threatening toxic effects produced by this drug, implying that these effects were produced by the drug itself.¹

The toxicity of novel compounds falls into two broad categories. First, toxic effects such as acute liver injury, leukopenia, cardiac arrhythmia, or rash may be related to the new drug molecule itself but unrelated to its intended mechanism of action. Considerable efforts are made to identify these types of toxicity *in vitro* and through studies in animals. However, our incomplete understanding of the mechanisms underlying such toxicity and the limitations of animal models inevitably mean that some potentially serious toxic effects go undetected in preclinical screening, and sometimes even during the full development process, and such drugs may reach the market, particularly if the toxic effect is rare

or occurs in only some subpopulations.

The second type of toxic effect results from the action of the drug on its intended biologic target. Such effects are always unknown when a target is “drugged” for the first time — and there must always be a first time. It is fortunate that the first pharmaceutical antagonism of beta-adrenergic receptors, histamine H₂ receptors, and angiotensin-converting enzyme in humans all proceeded satisfactorily. Until these targets had been manipulated by drugs, many aspects of their biology were unknown. New drugs of the same classes that are developed subsequently, although still carrying the risk associated with new molecules, may be administered with greater confidence because of the knowledge base that has been built with previously studied drugs that have similar action. But when a compound addressing a new biologic target is tested for the first time in humans, much greater caution must be exercised. Such caution should include avoidance of treating multiple volunteers simultaneously or without a reasonably long interval between them. The effects of very low doses in the first subject should be monitored carefully for a period sufficient for the detection of both immediate and later adverse effects before the drug is given to additional volunteers. Had such a design been used in the TGN1412 study, fewer volunteers would have been injured, because the serious toxic effects would have been identified in the first volunteer.

In some cases, a phase 1 trial does not, in fact, represent the first attempt to manipulate a particular

biologic target — though the researchers may be unaware of previous efforts. Clearly, we should not be exposing people to such manipulation if it has been shown, in studies in either humans or animals, to carry serious risks outweighing any potential benefits. How would we respond if we were to learn that others had abandoned CD28 agonists similar to TGN1412 because they produced an overwhelming cytokine or immunologic response? This issue has become more pressing as drug development, particularly of new biologic compounds, has shifted to small biotechnology companies that lack the massive “memory” of the large, integrated pharmaceutical companies that have historically developed most drugs. Unfortunately, the companies that generate early safety data consider them proprietary — a concern that must somehow be reconciled with patients' safety. Volunteers rightly expect that we put their safety before competitive advantage, and researchers have an ethical obligation to prevent the exposure of additional volunteers to previously identified risks.

How can we improve the knowledge base for designing trials of new drugs directed at novel targets and make it available to developers and regulators when they are considering the safety of such trials? One approach would be to ensure that all data from preclinical drug research are held in a secure database, indexed by biologic target, and accessible only by major regulatory authorities, which are used to handling confidential data. Registration of trials and storage and retention of such data in a format accessible to reg-

ulators — regardless of what decision was made regarding continued development of the molecule — would increase the safety of future studies. If this system were designed not to be so intrusive as to inhibit innovation but nonetheless to provide sufficient transparency, it would help to ensure that safety lessons need not be relearned repeatedly. Indeed, it is difficult to imagine how regulators can currently approve phase 1 studies without access to such data in a readily searchable format during the review process.

The details of this trial, including such crucial facts as the dose, rate of drug administration, planned number of doses, intervals between doses, and even whether multiple doses were received by any volunteer, were initially kept confidential under current laws in the United Kingdom. The MHRA has now decided to release the details of the trial, including its protocol,¹ which makes clear that the intent was to study four groups of eight volunteers with each group receiving progressively higher doses; two volunteers in each group were to

receive placebo. Only the first group was studied. However, this incident once again raises the question of whether such trials should be registered in an accessible database such as ClinicalTrials.gov.⁵ There are fundamental questions about which, if any, details of a clinical trial involving volunteers should ever be confidential or whether safety and ethics principles can be ensured only by an open, transparent process in which such trials and protocols are registered in a public database. This issue has become more urgent in the light of both this recent incident and the migration of clinical trials to less developed countries, where oversight may be less rigorous.

Although it is important to emphasize that most phase 1 studies have been safe, it is equally important to ensure that lessons are learned from this experience and systems put in place to minimize the risk of recurrence. We must not squander the experience of the participants in such trials by failing to share the knowledge gained with their help. We have an opportunity to learn from events

in the TeGenero study how to improve early drug evaluation, and we clearly need to do so as we develop more and more new compounds. Academia, the pharmaceutical and biotechnology industries, and regulators must work together to prevent such clinical-research nightmares from happening in the future.

An interview with Dr. Wood can be heard at www.nejm.org.

Dr. Wood is a professor of medicine and pharmacology at Vanderbilt University School of Medicine, Nashville. Dr. Darbyshire is the director of the Clinical Trials Unit of the Medical Research Council, London.

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2. North West London Hospitals press statements. (Accessed April 13, 2006, at <http://www.nwlh.nhs.uk/news/item.cfm?id=97>.)
3. Stein CM. Managing risk in healthy subjects participating in clinical research. *Clin Pharmacol Ther* 2003;74:511-2.
4. Raper SE, Chirmule N, Lee FS, et al. Fatal systemic inflammatory response syndrome in an ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol Genet Metab* 2003;80:148-58.
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Compensation for Injured Research Subjects

Robert Steinbrook, M.D.

Two recent developments — increased awareness of the complications that may follow egg donation for stem-cell research and the disastrous consequences of a clinical trial of the humanized monoclonal antibody TGN1412 in which healthy volunteers nearly died (discussed above by Wood and

Darbyshire) — have focused renewed attention on the long-standing issue of compensation for injured research subjects.¹ In the United States, despite decades of discussion and recommendations by national commissions, sponsors and institutions are not required to provide either free med-

ical care or compensation, although some do. In contrast, many European countries mandate the provision of clinical-trials insurance, through which subjects are often covered regardless of fault.

Participation in clinical trials always carries some risk, but serious injury or death is rare, partic-