Severe adverse reactions prompt call for trial design changes

Susan Mayor *London*

Drugs from new chemical or biological classes being tested in phase I trials—the earliest trials of a new drug in humans—should be tested in only one person at a time, a specialist said after a UK phase I trial resulted in six healthy volunteers becoming severely ill.

The young men were taking part in the first study in humans of TGN1412, a fully humanised monoclonal antibody designed to bind to CD28, a cell surface molecule on T cells which play a role in a variety of cell mediated immune reactions. The drug was being developed for the treatment of autoimmune and inflammatory diseases and leukaemia by a German company, TeGenero.

The six volunteers developed severe reactions within three hours of being given TGN1412 intravenously, while two other men who were given a placebo showed no sign of illness. One of those who was given the placebo told the BBC that the men who became ill reported feeling cold before developing severe headache and swelling of the head and neck. They later developed multiple organ failure and needed intensive care.

Ganesh Suntharalingam, clinical director of intensive care at Northwick Park Hospital, London, where the volunteers were transferred after becoming ill, said that the drug had caused an inflammatory response that had affected “some organs of the body.”

Joe Collier, professor of medicines policy at St George's Hospital Medical School, London, said that giving a drug that had never previously been tested in humans to several people simultaneously was “madness.” One of the men who was given placebo in the trial said that the volunteers had been given the drug at 10 minute intervals.

Professor Collier said, “Any

drug is associated with some risk, even drugs from classes that have previously been tested or used in man. When you give a drug from a new class for the first time, the risk is unknown.” He said the best way to minimise this risk would be to give the drug to one person and observe any adverse effects before proceeding to give it to others.

“Giving a new drug to several volunteers within a short time was designed to be quick for the clinical research organisation but automatically put those given the drug at risk,” Professor Collier said.

Phase I trials are designed primarily to test the safety of a drug. They expose study participants to a much lower dose of the drug than was used previously in animal models, and the researchers observe the effects of the initial dose before increasing it. The trial with TGN1412 had been approved by the Medicines and Healthcare Products Regulatory Agency, the body that regulates clinical trials in the UK, and a local ethics committee.

A spokesperson for the agency said: “The protocol for the trial indicated that dosing was staggered over a relatively short period of time. The drug was given to one person, who was monitored. Then it was given to the next one.” However, she said that 80% of phase I trials did not use staggered dosing because the dose used was so low: usually 500 times lower than that tested in animals.

The agency is now leading an investigation into the incident. This will assess whether approved procedures were followed and will investigate the possibility that volunteers had been given an inappropriate dose or that the drug had been contaminated in some way, the spokesperson said.

A statement from Parexel, the US company that carried out the

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Thomas Hanke (left) of TeGenero said the drug had been tested on rabbits and monkeys. Myfanwy Marshall, girlfriend of one of the volunteers, said her boyfriend needed a miracle to recover

trial, said that an initial review had shown that the best practices had been followed. Thomas Hanke, chief scientific officer of TeGenero, said that TGN1412 had been “tested extensively in laboratories and on rabbits and monkeys with no adverse effects and no drug related deaths.”

Janet Darbyshire, director of the clinical trials unit of the UK Medical Research Council, said that the development of serious illness in all healthy volunteers exposed to a new drug was “unprecedented.” The Medicines and Healthcare Products Regulatory Agency agreed that it was “very rare.” It approves approximately 350 phase I clinical trials each year in the UK.

Professor Darbyshire added that the fact that TGN1412 is a fully humanised monoclonal antibody may make effects in animals—even in primates—difficult to translate to humans. Models involving genetically modified mice may offer a useful way of testing fully humanised antibodies, she said.

The incident also underlined the need for phase I clinical

trials to be conducted within easy reach of intensive care facilities. The trial was carried out in an independent clinical trials unit located on the campus of Northwick Park Hospital, a large teaching hospital. This made it easy to transfer the men to the hospital's critical care unit quickly after they became ill.

Herman Scholtz, head of Parexel International Clinical Pharmacology, said: “Such an adverse reaction occurs extremely rarely, and this is an unfortunate and unusual situation.”

Dr Suntharalingam said earlier this week: “We are continuing to make advances with treating... four seriously ill patients.

“The two other men are still in a critical condition. We are seeing some very early signs of improvement, but because of their complex and very serious condition it is still too early to comment on prognosis.”

Four of the six volunteers had improved enough to eat meals and talk to family members, by the time the *BMJ* went to press on Tuesday. (See Editorial p 677 and Personal View p 735.)