

Ethical Considerations in Phase I studies: TGN1412 Case

In March 2006, a Phase I study of a humanized monoclonal antibody designed to treat leukemia and rheumatoid arthritis captured the attention of not only the biomedical world, but also that of the public. The trial received intense and long-lasting media coverage because all six of the healthy male volunteers given the treatment in the trial suffered from immediate adverse reactions. All were hospitalized, at least four suffered from multiple organ dysfunction.

“SuperMAB”

TGN1412 (trademarked “superMAB”) is the first product of a small German pharmaceutical company TeGenero. It belongs to a novel class of synthetic antibodies; specifically, it is a humanized monoclonal antibody that is a strong agonist for the CD28 receptor of T cells. TGN1412 was thought to have the potential to revolutionize the treatment of leukemia and rheumatoid arthritis. The drug trial was carried out by Parexel, a Massachusetts-based company that helps bring new therapeutics to market for pharmaceutical and biotechnology firms.

Clinical Trial

Parexel began conducting the Phase I trials for “SuperMAB” in Northwick Park and St. Mark’s Hospital, London in March 2006¹. The plan was to recruit healthy male volunteers into the study and offer compensation of £2,000 (approximately \$3,200 USD) per participant, with an expected commitment to a three-day inpatient stay and a dozen outpatient visits over the period of a month².

The trial was a double-blind, randomized, placebo-controlled study. On March 13th, the treatment for the first cohort of eight healthy volunteers began: two received placebo and six received 1/500th of the highest dose used in previous animal experiments. All subjects were between the ages of 19 to 34 and were healthy at the onset of the trial. Each participant signed a consent form for participation in the study (see consent form here: http://www.circare.org/foia5/tgn1412_consentform.pdf).

Within 90 minutes of receiving a single intravenous dose of the drug, the six subjects who received TGN1412 experienced a systemic inflammatory response. Their response was described as a “cytokine storm”, an immune reaction that causes a sharp drop in white blood cell levels and can result in headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension³. Within 16 hours after infusion, all six participants became critically ill and were subsequently hospitalized.

All six subjects survived, but some of the men are expected to have long-term disabilities resulting from their injuries⁴.



The Medicines and Healthcare products Regulatory Agency (MHRA) confirmed that they had approved the trial, including the plan to give the initial dose to all six men in the first cohort within a short period of time⁵.

Discussion Questions

Consider the following questions as you start the discussion. You are encouraged to discuss about other ethical aspects of the case as well.

1. Please read the consent form, specifically page 6: “Possible Side Effects”. Do you believe that this accurately disclosed the risks of the trial? Would you have participated?
2. Do you think the compensation of £2,000 per participant for the study constitutes 'undue inducement'? Why or why not?

Please be respectful of others' opinions and the controversial nature of this case. As with all ethical issues, there is no one right answer.

Sources:

¹ “[Media Advisory: Parexel International Statement Regarding TeGenero AG Phase I Trial at Northwick Park Hospital, UK](#)” (Press release). Parexel. 2006-03-13.

² TGN1412 Consent form. http://www.circare.org/foia5/tgn1412_consentform.pdf

³ Suntharalingam G, Perry MR, Ward S, et al., “Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412”, *New England Journal of Medicine* 7 September 2006, vol.355, p.1018–1028.

⁴ Elephant Man drug victims told to expect early death. *The Sunday Times*, 30 July 2006.

⁵ “[Update to frequently asked questions regarding TGN1412](#)”. *TeGenero*. 2006-03-19. Archived from the original.