

Lessons from TGN1412

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The outcome of participating in a phase 1 clinical trial of the monoclonal antibody TGN1412 (CD28-SuperMAB) has been dreadful for the six men at Northwick Park Hospital. Two volunteers remain in a coma, and it is not certain they will emerge unscathed. The testimony of a trial participant who luckily received a placebo is more like a scene from a horror film than the normal public perception of clinical research. Understandably, this has led to widespread media coverage.

The reasons for this tragedy are still speculative. Potential dosing errors and problems in the manufacture of the product have been put forward. Some immunologists have suggested that the reaction is indicative of a flood of inflammatory cytokines, triggered by the drug's stimulant effect on T-cells. However, there are a few issues raised that are more general in nature.

The incident has led to the inevitable claim that testing drugs on animals is a waste of time. Yet events like this are extremely rare; all the patients taking active treatment had severe reactions. Animal testing of drugs does find toxicity and, without such tests, severe adverse effects in human test subjects would be more common.

Some are arguing that such testing in healthy humans should be stopped. However, without initial dosing studies in humans, eventual movement of a new drug to clinical practice would be impossible. New procedures in the area of biologicals, such as microdosing on small areas of a volunteer, may be a way forward.

Ethical arguments

Media coverage of this disaster might have led to falls in clinical trial participation, but research groups are reporting paradoxical surges in interest, and enquiries about the payments available. Some have argued that payment for participation in studies is a form of coercion, but would you participate for nothing? Is it unethical to pay volunteers who help achieve a moral good, such as the development of a new treatment for leukaemia? Also, motivations are not always purely financial: one of the men in the TGN1412 trial cited helping to increase scientific knowledge, as well as money he could earn.

The UK has an extremely rigorous system of ethical review and regulation. Ethics committees are focussed on the rights of participants in studies. One participant in the TGN1412 trial reported that the 15-page consent form was 'complicated' and he had to

rush to read the information. Perhaps more time for the decision to participate is required, similar to the cooling-off period seen in financial agreements.

Some commentators have expressed unease that a private company was performing clinical trials within an NHS establishment. As the NHS is not in the expensive business of developing new drugs, having neither the skills nor the ability to risk huge sums of capital to such ends, virtually all drug research involves private companies; otherwise, new drugs would never reach the market. Even if this had been a publicly-funded trial, it would have followed the same process as a private company. It is not clear what additional safety benefit an NHS-run trial would have brought.

The TGN1412 trial may well lower public trust in the pharmaceutical industry. In a climate influenced by the MMR controversy, the widespread plaudits for the film *The Constant Gardener*, and a general distrust of large corporations, the TGN1412 trial represents yet another stone to grind an axe upon. Hopefully, it will provoke a more serious and considered debate about the risks society should take in developing treatments for serious life-threatening diseases.

Lessons to learn

The TGN1412 disaster is also a reminder that many new drugs being developed and used today are extremely powerful, working through mechanisms that are only just being fully understood. There may be lessons to learn for researchers, the pharmaceutical industry, regulators and even trial participants. Certainly, anyone entering a clinical trial in the wake of the TGN1412 controversy can no longer look upon study participation as a risk-free money-making carousel. It also underlines the importance of vigilance in the reporting of adverse effects of new drugs, particularly the new biological products, as they are used in wider numbers of patients for longer periods of time.

Be wary of those claiming that this case is representative of wider problems and be equally wary of those who think there is nothing to be learned.

For more information and discussion on this issue visit www.blacktriangle.org.

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