

*Risk Assessment for Clinical Trials
of Monoclonal Antibody*

-Focus on Non-Clinical Studies For FIM

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Response to TGN 1412 case

BBC NEWS BBC News in video and audio

News Front Page Last Updated: Wednesday, 15 March 2006, 09:52 GMT

Six taken ill after drug trials

Six men remain in intensive care after being taken ill during a clinical drugs trial in north-west London.

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction. The six are being treated at Northwick Park hospital.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.

An investigation has begun at the unit, run by Parexel, which said it followed recommended guidelines in its trial.

The men were being paid to take part in the early stages of a trial for the drug to treat conditions such as rheumatoid arthritis and leukaemia until they were taken ill on Monday within hours of taking it.

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Clinical trial final report

Press release

Date: 25 May 2006
Time: 12:47
Subject: Clinical trial final report
Contact: Press Office 020 7084 3535/3564 or press.office@mhra.gsi.gov.uk
Out-of-hours 07770 440 109

Following on from an interim report published by the Medicines and Healthcare products Regulatory Agency on 5/4/06 into the adverse incidents which occurred on 13/3/06 during the clinical trial of TGN1412 today been issued on the matter (see below).

In addition to the various inspections carried out by MHRA inspectors and the German Regulatory authorities, tests have been conducted on the drug product. The product testing focused on the batch used in the clinical trial as well as the batch used in the trial. Although there were some 'good clinical' discrepancies identified (see below), the conclusions remain the same as reported in April 2006: biological effect is the most likely cause of the severe reactions in the six trial volunteers.

"This is a very complex scientific issue, which will be reviewed by the independent expert scientists at the Secretary of State for Health. We are satisfied that the adverse incidents which occurred

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ORIGINAL ARTICLE

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti-interleukin-2 receptor antagonist antibody.

Summary
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CME Exam
Supplementary Material
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Perspective
by Sharpe, A. H.
Editorial

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EDITORIAL

Volunteers at Risk

Jeffrey M. Drazen, M.D.

Clinical research can be a risky endeavor. In this issue of the *Journal*, Suntharalingam et al.¹ describe the events that occurred when six healthy volunteers received a dose (0.1 mg per kilogram of body weight) of TGN1412 — a superagonistic humanized monoclonal antibody that stimulates and expands T-cell populations independently of the ligation of the T-cell receptor. In all six patients, the cytokine-release syndrome developed, including multicystic failure. Two of the patients required mechanical ventilation, and all received renal-replacement therapy. All six had severe hypotension, and peripheral ischemia developed in one patient to the extent that surgical treatment was required.

Analysis of the infused TGN1412 has, to this point, indicated that it met the specifications of the manufacturer — that is, it was sterile and pyrogen-free and contained the expected amount of protein without contaminants. Thus, the response observed is likely to represent a clear example of an idiosyncratic "cytokine storm" without the background of another illness. On the basis of the experimental data that had been gathered before the testing of this monoclonal antibody in humans, the biologic and subsequent physiological changes were unexpected. Also in this issue of the *Journal*, Sharpe and Abbas speculate on the biologic events that occurred when the patients received this treatment.² Although the data clearly show the occurrence of a cytokine storm, research is ongoing to determine exactly what happened and why. We

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