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Learning from the TGN1412 trial

This experience should foster an open culture in medical research

See also *News* p 683 and *Reviews* p 735

Earlier this month eight healthy volunteers in a phase I trial received a T cell agonist at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London.[1] The six men who received the active component rapidly developed catastrophic multisystem failure; the remaining two, who received a placebo, were unharmed. At the time of going to press, two remained in a critical condition. This was the first human trial of TeGenero's TGN1412, a new humanised monoclonal superagonist of the CD28 T cell surface receptor,[2] designed to mitigate autoimmune and immunodeficiency disease.

This allegedly unprecedented event in clinical research represents a very human tragedy, one which will probably change for ever the face of clinical drug development and testing, and one which gives us the opportunity to learn many valuable lessons. A system based approach to learning is more likely to generate useful outcomes than one that is narrowly explanatory and blame oriented. Yet health care has been learning this lesson slowly and painfully.[3] Nobody should be surprised that this disaster happened: even rare events have finite probabilities.[4]

Questions raised by the trial

While inquiries such as that of the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) continue, information about the TGN1412 trial remains fragmentary and often second hand. But some broad questions have arisen.

How were the volunteers recruited and motivated? With every death of a healthy volunteer, such as Ellen Roche (a 24 year old healthy volunteer who died during a study on acute asthma at Johns Hopkins University, Baltimore), we are assured that this will never happen again, and yet it continues to do so. How much accurate information, based on full risk analysis, do volunteers receive? The uncertainties of medicine are rarely greater than when new drugs are first administered to humans. The necessity to anticipate rare events has to be equally high, therefore, and the process of obtaining informed consent must emphasise the possibility of severe injury or death. Interviews with the victims of the TGN1412 trial and their families have yielded the expected myriad of motives, including altruism, but monetary reward played an equally important role. How much money is too much, and when does money cloud the judgment needed to evaluate risks realistically?

Why was the drug tested on healthy volunteers rather than patients? Phase I trials in healthy volunteers raise special ethical issues when the benefits are non-existent and the risks are high. This was especially important in this trial, in which an agonist drug targeted at compromised immune systems was given to individuals with intact immune systems. The potential for the sort of cytokine storm described by the company on its website (www.tegenero.com) is of more than theoretical interest.

Why were all eight volunteers given the drug at the same time? Several observers have asked whether minimal standards should include observing a single dose in a single carefully monitored individual, rather than relying solely on dose as a function of animal lethality.

What information did the ethical and regulatory bodies have about the trial? How much do regulatory and ethical bodies have to rely on information from investigators and sponsors, which may be subject to publication bias, rather than truly independent reviews? Several prominent immunologists have claimed that not only was this trial theoretically flawed but that published evidence—both from commentaries on preclinical testing data and from clinical data on similar drugs (such as MDX-010, a CLTA4 antagonist)—raises questions about how such reviews are performed.[5]

Medicine has advanced, traditionally, on the back of the increasingly genetically modified white mouse (and the occasional male medical student). With increasing sophistication of molecular targeting using specific human receptors, the applicability of the mouse as a model for human physiology becomes questionable. The CD28 T cell surface receptor, the target of TGN1412, shares only 68% of identity of amino acids between mouse and man.[6] Relative lack of severe toxicity in animal models should never be construed as a guarantee of safety in man, as the story of thalidomide taught us.

A more transparent culture

Finally, what does this trial tell us about the degree of transparency throughout the process of developing new drugs? Many groups have called for mandatory registration and disclosure of clinical trials and their protocols.[7 8] Had this trial been available for public review, potential problems might have been identified and avoided. Despite claims of the need to protect competitive advantage, public interest overwhelmingly requires that all information about this drug and this

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trial should now be made publicly available immediately. Lives are at stake and there can be no possible reason, save liability, for secrecy. We have been assured repeatedly that proper procedures were followed, when the real question is whether they were the right procedures.

This tragedy creates one more imperative for an open culture in medical research, a culture that many fear is increasingly losing its way.[9–11] There must be an immediate moratorium on CD28 research in humans until we have a better understanding of the potential for harm. Furthermore, only an independent inquiry can restore public and professional confidence: the MHRA is compromised by its own role in regulating trials. Such an inquiry must have a broad remit, including the social, political, legal, and economic forces shaping new drug development. Its recommendations should consider mechanisms for an immediate centralised response to unexpected events—such as those at Northwick Park—from the global scientific community.

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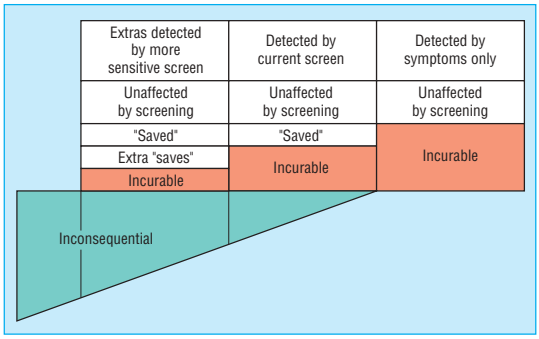
Evaluating new screening tests for breast cancer

May require randomised controlled trials to assess overdetection

The use of magnetic resonance imaging to screen women with high risk mutations in the genes associated with breast cancer has raised debate on what constitutes sufficient evidence for the efficacy of new screening tests.[1-4] The gold standard is evidence from randomised trials that early detection reduces mortality, as is the case for mammography and breast cancer,[5] but how should we evaluate new tests that might detect cancer earlier?

Showing that a new test is more sensitive than others suggests that it has promise as a possible screening test,[6] but detecting more apparent cases does not necessarily mean that using the test routinely will lead to a further reduction in breast cancer deaths. To fulfil the criteria for an effective screening test, the additional cancers detected must include ones that would both progress during the patient's lifetime and be curable by earlier treatment. The extra cancers picked up by new tests may count as cancers histopathologically but might not progress to cause symptoms in the women's lifetime: thus, a new test might lead to more overdetection rather than improved outcomes (figure). Overdetection of ductal carcinoma in situ (DCIS) is well documented,[7] but it may also occur with cancers that seem, histologically, "invasive."[8 9] Overdetection may cause harm through unnecessary labelling and treatment of patients as having a cancer that, without screening, might never have been diagnosed.



Balance between deaths averted and overdetection by more sensitive test

Overdetection can be identified best in a randomised controlled trial. Screening for several years should yield a higher average incidence of cancer in the screened group than in an unscreened control group during the years of screening. Once screening stops, the annual incidence of cancer in the screened group should drop below that in the unscreened group, and the eventual total number of cancers detected in the groups should equalise.[10] A persisting excess of cancers in the screened group represents overdetection, as shown in the Malmö mammographic screening trial, for which the estimate of overdetection in women aged 55-69 at randomisation, followed for 15 years after the end of the trial, was 10% for all breast cancers and 7% for invasive breast cancers.[11]

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