

On the Net... Drug Testing, Adverse Reactions, and the TGN1412 Disaster

by Karen Shashok

Internet coverage of the TGN1412 Phase 1 trial disaster, 20 March to 29 April 2006.

Compliance with the protocol, ethics committee approval and informed consent were not enough to protect healthy volunteers for a phase 1 trial in a London hospital from life-threatening cytokine release syndrome, which nearly killed two of the first human recipients of a new biological agent. The patients' clinical ordeal, attempts to explain the severe adverse reactions, and experts' discussions of what should be done to prevent similar mishaps were quickly covered on the Internet. If you're in a hurry for more information about the catastrophic failure of the TGN1412 phase 1 clinical trial, I recommend the weblog run by Health Care Renewal [1], the collection of UK and US news clippings compiled by the Alliance for Human Health Research Protection [2], the Black Triangle blog run by Anthony Cox [3], and the Wikipedia entry for TGN1412 [4]. If you want a broader overview of web coverage, read on. This review does not cover all the issues this case raised, but looks at some of the most informative sites and singles out a few highlights, as well as a few missed opportunities to use the Net to best advantage.

What happened?

On 13 March 2006, a monoclonal antibody designated TGN1412, developed by the German biopharmaceutical firm TeGenero AG (founded by researchers who discovered the "superagonistic" mechanism of action of certain monoclonal antibodies), began its first phase 1 trial at the clinical pharmacology unit operated by contract research organisation (CRO) Parexel International in Northwick Park Hospital, London. Eight paid volunteers were given an injection; six received the active agent, two were given a placebo. Within hours (or minutes, according to some reports) each of the six men who received the drug became critically ill with multiple organ failure; their lives were saved because they were already in hospital when their symptoms appeared, and so were immediately given high-quality care. Two of the men fell into a coma that lasted 8 days in one case and nearly 3 weeks in the other. As of late April 2006, all patients were recovering from the cytokine release syndrome triggered by TGN1412, but one was expected to lose some fingers and toes to dry gangrene, and the long-term sequelae (if any) in the other volunteers had not been made public. Neither TeGenero nor Parexel had posted any updates about the incident since 5 April 2006.

The monoclonal antibody was designed to stimulate regulatory T cells of the immune system via surface receptor

CD28, and had been approved for phase 1 testing by the UK's Medicine and Healthcare Regulatory Agency (MHRA) and the local ethics committee. The protocol had reportedly been followed correctly, although reports varied regarding the timing of administration of the dose to successive participants. Not all specialists concurred in hindsight, but toxicology studies done before testing in humans had seemingly not given any warning that such a severe adverse reaction might ensue.

The MHRA immediately investigated the incident, and in early April concluded that the adverse reactions were most likely caused by an unpredicted biological action of the drug in humans, ruling out errors in manufacture, formulation, dilution or administration. The UK Secretary of State for Health announced it would establish a group of international experts to study how the case could affect clinical trial regulations worldwide. In the interim, the MHRA will require additional expert opinion to rule out the possibility of similar adverse events for first-in-human trials of any monoclonal antibody or other novel molecules that target the immune system. How the incident will change procedures for approving phase 1 trials of biologicals remains to be seen.

What was useful about Internet coverage?

Coverage of the TGN1412 phase 1 disaster on the Internet quickly provided several different angles on the story. Although rather little information was provided by TeGenero [5], Parexel promptly issued a media advisory about the adverse reactions, with frequent updates and a list of FAQs about TGN1412 [6]. The hospital where the trial was run also issued press releases on its website [7].

News articles initially emphasised concerns for the patients' lives and reflected health authorities' surprise at the adverse reactions, which were completely unforeseen. When the MHRA investigation found no error on the part of the manufacturer of TGN1412 or Parexel, later articles wondered how the mishap could have occurred despite the fact that all appropriate regulations had been followed and all necessary permissions had been obtained. Editorials in medical journals called for greater transparency in the process of developing new drugs. As Goodyear noted in the *BMJ*, "We have been assured repeatedly that proper procedures were followed, when the real question is whether they were the right procedures" [8]. Commentators concluded that although the clinical protocol had been implemented correctly and all oversight measures had been followed, the oversight process itself was not sophisticated

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enough to detect the risk to humans of testing a monoclonal antibody designed to “override” the immune system.

Blogs to the rescue

Some of the most up-to-date information and insightful discussion about the case were found on weblogs run by people familiar with health care and the pharmaceutical industry. Postings on Health Care Renewal, run by Dr RM Poses [9–14], raised several issues ahead of journals and news agencies, and this may have been the first source to call publicly for “complete transparency about the drug or device to be tested, and how testing will be performed and supervised.” Other postings on this blog summarised information published in the press and journals, and editorialised on their implications for the drug and device industry, informed consent procedures and approval of phase 1 trials for new biologicals.

A couple of threads on the Black Triangle blog (maintained by Anthony Cox, MRPharmS) also contained judicious evaluations of the failed trial and the MHRA interim report [15]. Interestingly, one of the bloggers who responded to the initial posting [dsquared, posted 8 April 2006] thanked Cox for his “hard work updating the Wikipedia entry on this subject.” Indeed, the Wikipedia entry for “TGN1412” was packed with clearly written information on the experimental drug and the events surrounding the adverse reactions [4]. Cox later reported the partial recovery of the last of the patients to be moved out of critical care, several days after the media’s attention had turned elsewhere [16]. His editorial on the failed phase 1 trial, published in *Prescriber* on 5 April and posted on the blog on the same day, is, however, gentler on the pharmaceutical industry than the debate that took place on Black Triangle [17, 18].

Random John reloaded [19], a blog run by a biostatistician who worked in the pharmaceutical industry before he became interested in alternative medicine [20], frequently tracks information about the drug industry. The postings here—many from experts, with only a few of the more inane sort of messages some blogs attract—were lucid and contained interesting links. “Random John” provides biographical information about himself that enables readers to decide how biased (or objective) his postings on health care, the drug industry and other scientific matters are likely to be—an example that ought to be imitated more widely.

Calls for transparency heeded

Both the CRO and the MHRA were criticised for not making public the consent form Parexel had used for this phase 1 trial, and questions were later raised regarding whether the risks of the study had been explained clearly enough to participants [21]. The Bloomberg news agency, cited by Health Care Renewal as the source of information on the consent form, faulted the risk-disclosure form on several points and noted that Parexel had “declined requests to release the document,” adding ominously that TeGenero “says it doesn’t have a copy to provide.” Eventually the informed consent form was made available, along with many other documents relating to the case, by Citizens for

Responsible Care and Research [22]. Meanwhile the case stirred anew suspicions that CROs, their clients, and even regulatory agencies might be cutting corners in order to speed approval for new drugs. At the time of this writing, documents relating to the phase 1 trial, including the clinical trial assessment report, investigator’s brochure, investigational medicinal product dossier and protocol, had been released on the MHRA website [23].

Newspapers, magazines and news agencies

As media attention turned toward analysis of the causes and consequences of the mishap, the Bloomberg news agency joined many online sources in concluding that existing mechanisms of scientific and ethical oversight for risky phase 1 trials were inadequate, and in suggesting that the commercial nature of CRO operations in general may undermine ethics and transparency. One article [21] noted that a previous investigation by the agency found “conflicts of interest and lax oversight in the US for-profit drug-testing industry,” but missed a golden opportunity to include a link to that story.

New Scientist’s coverage emphasised immunological aspects of the drug’s effects, and was the first to report on information available in the scientific literature about the possible risk of non-specifically activating natural killer T cells [24], an angle that the Times Online also quickly pursued [25]. The weblinks provided with this and an earlier *New Scientist* article dated 15 March [26] were generally useful. Coverage of the case by the Guardian Unlimited was timely if somewhat superficial, and the links in their articles were generally less useful because they tended to link to sources about medicine and health, but not to pages that contained up-to-date information specifically on the TGN1412 case. An early article on the case in the Times Online did a fine job of giving readers enough accurate background information about clinical trials so they could grasp the importance of the TGN1412 failure, and made technical information understandable for lay readers without oversimplifying things [27].

In an article uploaded on 20 March, the Breitbart news agency [28], which compiles news from Reuters, Associated Press, AFP and the Drudge Report, cited Janet Derbyshire, head of the clinical trials unit of the British Medical Research Council, as saying that the accident could not have been avoided with current testing methods. The article suggested that better ways to assess the safety of new drugs might involve laboratory animals genetically modified with human genes, using miniscule doses in a part of the body “isolated” from the rest of the body, testing new drugs in one person at a time rather than several simultaneously, or allowing compassionate use in patients with the condition the drug is intended to treat (which would amount to using a cohort design rather than a randomised design).

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Ethics and economics

Under the heading “Medical Wonder Drugs” [29] former US congressman turned news writer Martin Frost posted a series of articles about the TGN1412 trial that touched on big issues (such as how regulatory oversight has become difficult given the “sheer volume and complexity of modern drug cures”) as well as specifics concerning the drugs’ mechanism of action in experimental animals and humans, with an interesting detour into the history of legal and ethical measures to protect human guinea pigs. Like Frost, other sources wondered whether the MHRA might be hampered by conflicts of interest. DrugResearcher.com cited and linked to a parliamentary select committee report filed a year before the TGN1412 calamity that “casts doubts on whether the MHRA should be investigating itself” [30]. According to the report, “[t]he organisation has been too close to the industry, a closeness underpinned by common policy objectives, agreed processes, frequent contact, consultation and interchange of staff.” This report, like an article from the excellent collection compiled by Alliance for Human Research Protection, suggested that the MHRA could not objectively investigate Parexel’s role in the events because “The organisation, process and techniques of the MHRA are focussed on bringing drugs to market fast.” Another ethical concern raised by the parliamentary report was the possibility that participants in clinical trials were sometimes given “limited information” and exposed to “unacceptable risks” [31].

Several sites worried that more lax ethical guidelines in the UK than in other countries might be attracting clinical trial business that stricter countries have eschewed. On 19 March, a Times Online article said, “[r]ecruiters favour the UK because the regulatory process here is seen as speedy. To critics, the regime is also inadequate” [32]. An item in the Wiley-produced website Pharmafocus.com that provided the points of view of major pharma and biotech industry groups in the UK observed that “[t]he UK is home to around half of all Europe’s phase 1 studies, and some fear disproportionate safety measures could be put in place, potentially undermining the country’s research base” (and possibly scaring away lucrative clinical trial business?) [33]. Mathaba.Net, citing an article published on 19 March in The Independent, reported that Parexel’s application for institutional review board approval for a phase 1 trial of TGN1412 at a German centre had been denied because of ethical deficiencies [34]. (On 26 April 2006 Google found about 288 hits for “IRB shopping.”) The recruitment pitch used by Parexel was quoted on many websites because it gave the impression that voluntary participation in the phase 1 trial for TGN1412 was akin to a paid holiday in restful, entertaining surroundings, with free food, no housekeeping responsibilities, and plenty of time to relax, watch digital TV, play video games or pool, use a DVD player, and enjoy free Internet access [35]. Despite media reports of the extreme distress and critical illness the vol-

unteers experienced, several sites noted the paradoxical surge in interest in volunteering for clinical trials, since information about the payments volunteers sometimes receive figured prominently in media reports. [36].

The implications of the disaster for future efforts to develop therapeutic monoclonal antibodies were the subject of an item on Pharmaceutical Business Review Online. As a “PBR Staff Writer” noted, “The indications for which TGN1412 was targeted, namely oncology and immune and inflammatory disorders, are areas forecast to see the strongest growth, and the trend toward [...] humanised products, rather than murine and chimeric antibodies, is also expected to gain momentum [...]. The high-profile failure of TGN1412, a drug candidate that falls within the most promising sub-categories of this new drug class, could have negative implications for drug development within this sector” [37].

Conclusion

The Internet enabled institutions put under pressure by the adverse reaction—the manufacturer of the new drug, the CRO hired to run clinical trials, the hospital where the volunteers were treated, and the UK drug regulatory agency MHRA—to quickly disseminate their press releases and the results of their own internal investigations. Errors in the manufacture or administration of the drug were ruled out, and the cause of the severe adverse reactions was identified by exclusion as the experimental drug itself. Immunologists and ethicists could then turn their attention swiftly to a review of the scientific literature to search for information that might explain why TGN1412 triggered cytokine release syndrome. Earlier research reports were soon found that suggested this possibility, raising new questions over whether the phase 1 trial that almost killed six men should have been approved. Internet dissemination of calls for more transparency was probably a factor in decisions to release documents about the trial to the public. Regulatory agencies, health authorities, ethics committees, and especially clinical trial sponsors, organisers and would-be participants are now awaiting the outcome of efforts this incident has spurred to improve the oversight of phase 1 or first-in-human trials of biological agents.

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Note: The MHRA released its final report on the trial on 25 May; see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023822&ssTargetNodeId=389 and references 5 and 7.

Grammar comes naturally

Surprisingly some fundamental characteristics of grammar are common to all languages. Researchers at the University of Rochester, USA, lead by Elissa Newport, studied gestures made by three deaf Nicaraguan boys. The boys had independently developed their own gestural-based language at home. Their 'home sign systems' were not influenced by any spoken language because they had been deaf since birth, or from any written or sign language because they had received no formal education.

The boys watched 66 short videos after which they explained what they had seen by using their home sign gestures. Each of the boys were found to have created a grammatical component for 'subject' which they used in the same form as highly evolved languages use it. The concept of 'subject' is complex because it can be the instigator (active) or the recipient (passive) of action in a sentence. That the boys developed the 'subject' concept without any outside linguistic influence and used it in the same way as other languages use it indicates humans have an innate ability to develop such grammar concepts. The researchers are continuing their search for further innate aspects of language.

It was Newport who established that there are crucial times in children's development when they are primed to learn languages after which this ability declines.

Source: Newport EL, Coppola M. Grammatical Subjects in home sign: Abstract linguistic structure in adult primary gesture systems without linguistic input. *Proc Natl Acad Sci U S A*. 2005 Dec 27;102(52):19249-53