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Giving monoclonal antibodies to healthy volunteers in phase 1 trials: is it safe?

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Many monoclonal antibodies (MAbs) have been studied in healthy volunteers in phase 1, but few data have been published on the safety of that practice. We aimed to review the available data, and thereby to estimate the risks of participation in phase 1 trials of MAbs. We searched PubMed, the ClinicalTrials.gov database and Google, using the search terms 'monoclonal antibody', 'phase 1' and 'healthy volunteers'. We identified 70 completed trials of MAbs in healthy volunteers, but the published data were too sparse to allow confident assessment of the risks of MAbs in healthy volunteers. Our best estimate of risk of a life-threatening adverse event was between 1 : 425 and 1 : 1700 volunteer-trials, but all such events occurred in a single trial (of TGN1412). In a phase 1 trial of a small molecule, the risk of death or a life-threatening adverse event appears to be 1 : 100 000–1 000 000 volunteer-trials, which is similar to the risk of many ordinary daily activities. Most people would consider that level of risk to be 'minimal' or 'negligible' and, therefore, acceptable. On that basis, the safety record of MAbs in healthy volunteers has been ruined by the TGN1412 disaster. However, that experience is unlikely to be repeated, because of improvements in governance and practice of phase 1 trials. If the experience of TGN1412 is disregarded, it seems reasonable to continue using healthy volunteers in phase 1 trials of MAbs, provided that there are scientific and medical reasons to conclude that the risk is truly minimal.

Introduction

In the European Union and USA, 28 therapeutic monoclonal antibodies (MAbs) are currently approved and three are being considered for approval [1]. Only six of those licensed MAbs were first given to healthy volunteers.

The risk of life-threatening adverse reactions in first in human (FIH) trials of MAb was brutally exposed by the TGN1412 incident [2, 3], yet MAbs continue to be given to healthy volunteers in phase 1. In this article, we review the published safety record of MAbs in healthy volunteers, and try to estimate the risk of severe injury or death, with the aim of reaching a conclusion on whether MAbs are safe enough to give to healthy volunteers in phase 1 trials.

Background

The first MAbs to be licensed were derived from mice and caused serious immune-mediated toxicity. The adverse effects of murine MAb therapeutic agents restricted their clinical development to indications with high morbidity and/or mortality (oncology, graft *vs*. host disease, transplant rejection, for example), and FIH trials were confined to patients. Improved genetic engineering techniques have allowed the development of chimeric, humanized and fully human MAbs, which cause fewer immune reactions. That advance in technology, together with other important factors including better choices of antibody and target antigen, have contributed to the success of MAbs. Their use has expanded into many therapeutic areas, particularly chronic inflammatory disorders such as rheumatoid arthritis and Crohn's disease.

Why use healthy volunteers?

Using healthy volunteers rather than patients in phase 1 trials has some important advantages. Trials can be done less expensively and more rapidly, because there is a plentiful supply of subjects, healthy volunteers are physically more robust, and may withstand and survive adverse

events better and it is easier to obtain frequent blood samples for pharmacokinetic and pharmacodynamic purposes. Healthy volunteer data may also be used to support more than one potential indication and comparative placebo treatments are ethical.

In a typical dose-escalating, FIH trial of a MAb, the first few dose levels may well be sub-therapeutic, yet might be immunogenic [4]. In theory, at least, such an immune response could impair a patient's response to higher, therapeutic doses. That might seem to favour the use of healthy volunteers in the FIH trials. However, there is a small risk that a healthy volunteer might be immunised against a MAb from which he might hope to derive benefit later in life. Indeed, when the first MAbs were developed there was serious concern about their possible immunological adverse effects in healthy volunteers. That concern does remain to some degree, but the risk has certainly been mitigated by the development of humanised and fully human MAbs, which are less antigenic than murine MAbs.

Why use patients?

MAbs have much longer terminal half-lives than do most of the 'small molecules' tested in phase 1. As a result, a single parenteral dose of most MAbs leads to prolonged systemic exposure, equivalent to that achieved in a repeat dose trial of a typical small molecule. Subjects are routinely exposed to the MAb for 8–10 weeks, before the safety and tolerability of a few days' exposure have been established.

When a new MAb is developed, its long term immune-mediated toxicity may be hard to predict. Sinister effects of MAbs identified to date include autoimmune disease, cardiotoxicity, malignancy and reactivation of latent infections, such as tuberculosis and progressive multifocal leucoencephalopathy [5–7]. Our ability to predict such effects has certainly improved, but it does not yet match our ability to predict the toxicity of small molecules. Principal investigators tend to have a background in general medicine, and lack expertize in immunology, so are dependent on others to help judge the safety of proposed MAb administration.

The pharmacokinetic properties of a MAb may differ greatly between healthy volunteers and patients with the target disease, because the pharmacokinetics often depend in part on the amount of target ligand present. Healthy volunteers usually express the target ligand or receptor to a much lesser degree than do patients, or may not express it at all. So, a phase 1 trial in healthy volunteers may yield pharmacokinetic information that is unhelpful because it is not predictive of what will be seen in the disease state. A further possible limitation of trials in healthy volunteers is that it may be impossible to measure the direct pharmacodynamic effect of a MAb if the target pathway is not expressed [8, 9].

Because of these considerations, for some novel MAbs phase I trials in patient populations may be the only reliable way to assess safety, tolerability, pharmacokinetics and pharmacodynamics. A further incentive to use patients is that they have the target disease, and so (unlike healthy subjects) have at least a chance of benefiting from the treatment. Finally, the lack of animal models that predict immunotoxicity in humans has discouraged the use of healthy volunteers. Nevertheless, many MAbs have been given to healthy volunteers in phase 1 trials in the past, and such trials continue to be done.

Trials of 'biosimilar' MAbs are rapidly increasing in number, and these may be regarded as FIH trials because different manufacturing processes can lead to minor differences in conformation of the final molecule. However, prediction of the risks of 'biosimilars' is more reliable than for novel MAbs, because the on-target effects should be the same as the original molecule. Therefore, sponsors may feel justified in enrolling healthy volunteers for these trials, and regulatory authorities may endorse that policy; but endorsement by a regulatory authority does not mean that the policy is safe and ethically justified.

We review here the evidence that is available to support administration of MAbs to healthy volunteers in phase 1 trials.

Methods

We searched PubMed, the ClinicalTrials.gov database and Google using the search terms 'monoclonal antibody', 'phase 1' and 'healthy volunteers'. We did supplementary searches in Google, using the name or code number of the drug, to gather additional information as necessary. We also searched the GSK Clinical Study Register [10], for GSK MAbs. Our searches included trials completed before the end of August 2012.

Results

We identified 70 completed trials of MAbs in healthy volunteers. Of those 70 trials, 44 were listed on ClinicalTrials.gov. The results of only six of those 44 trials had also been published in a medical or scientific journal; further information on 4 of the unpublished trials was available on the internet and GSK Clinical Study Register. The PubMed search identified a further 16 trials in addition to those listed on ClinicalTrials.gov, and the Google search identified a further 10 trials.

Table 1 lists the published phase 1 MAb trials in healthy volunteers that we found. In the published trials involving 36 MAbs, a total of 1799 healthy volunteers were dosed with MAb or placebo.

No deaths were reported, but six life-threatening adverse reactions were identified: all six occurred in a

Table 1

Completed phase 1 MAb trials in healthy volunteers identified by our review

Reference	MAb	Number of healthy volunteers
[35]	(99 m)Tc-DI-DD-3B6/22-80B3 Fab' (anti-D-dimer MAb Fab' fragment)	32
[36, 37]	Abciximab (anti-glycoprotein IIb/IIIa receptor Fab)	36 30
[38]	AMG 317 (anti-interleukin-4 receptor MAb)	60
[39]	Anti-CD18 F(ab')2 fragment	53
[40]	Anti-interleukin-10 MAb	10
[41]	Anti-Shiga toxins type 1 and 2 MAbs	26
[42]	ASKP1240 (anti-CD40 MAb)	104
[43]	B-E8 (anti-IL-6 MAb)	24
ClinicalTrials.gov	Belimumab (anti-B-cell activating factor MAb)	118
[44]	c alpha Stx2 (anti-Shiga toxin type 2 MAb)	17
ClinicalTrials.gov	Canakinumab (anti-interleukin-1 beta MAb)	20
[45]	CDA-1 (anti-*Clostridium difficile* toxin A MAb)	30
[46]	CMAB007 (anti-immunoglobulin E MAb)	36
[47]	Fanolesomab (anti-CD15 MAb)	30
[10]	GSK249320 (anti-myelin associated glycoprotein MAb)	46
[48]	GSK679586 (anti-interleukin-13 MAb)	56
[49]	IC14 (anti-CD14 MAb)	16
[50]	KBPA-101 (anti-*Pseudomonas aeruginosa* serotype O11 MAb)	32
[51]	MAb C23 (anti-cytomegalovirus MAb)	20
[52]	MDX-1303 (anti-*Bacillus anthracis* MAb)	46
[53]	MEDI-528 (anti-interleukin-9 MAb)	53
[54]	MGAWN1 (anti-West Nile virus MAb)	40
[55]	Motavizumab (anti-respiratory syncytial virus MAb)	30
[56]	PAm (anti-*Bacillus anthracis* MAb)	105
[57]	R297 (anti-Rhesus factor D MAb)	25
[58]	Raxibacumab (anti-*Bacillus anthracis* MAb)	333
[59]	REGN727(anti-proprotein convertase subtilisin/kexin 9 MAb)	72
[60]	Rovelizumab (anti-CD11/CD18 MAb)	20
[61]	RSHZ19 (anti-respiratory syncytial virus MAb)	26
[62]	SB 249417 (anti-factor IX MAb)	26
[63, 64]	TB-402 (anti-factor VIII MAb)	24 56
[65]	TCN-032 (anti-influenza virus MAb)	40
[66]	Tefibazumab (anti-*Staphylococcus aureus* MAb)	19
[2]	TGN1412 (anti-CD28 MAb)	8
[67]	TRX1 (anti-CD4 MAb)	9
[68, 69]	YM337 (glycoprotein IIb/IIIa inhibitor)	53 18

Fab fragment antigen-binding region of a MAb.

single trial that involved the first administration of TGN1412 to humans. The outcome of the trial was reported in great detail [2, 3]. TGN1412 is an anti-CD28 MAb superagonist which directly stimulates T lymphocytes. It was given intravenously to six healthy male volunteers at short intervals. Within a few hours after dosing, all six men developed a systemic inflammatory response with early lung involvement, vasodilatation, increased vascular permeability, hypotension and tachycardia, after variable prodromal features. Despite treatment with intravenous hydrocortisone, chlorphenamine and metaraminol, all six men required supportive treatment on an intensive care unit for multi-organ failure caused by cytokine release syndrome. The two worst-affected men required prolonged mechanical ventilation for adult respiratory distress syndrome (ARDS). One of these men had severe ischaemia of the extremities and developed patchy necrosis of his fingers and toes. All the men gradually improved over the course of many weeks, after empirical treatment with methylprednisolone and daclizumab (a MAb to the interleukin IL-2 receptor on T cells), and with supportive care. Although all six men survived, they did so only because of the excellence of the treatment they received: Two of the men clearly came very close to death and five of the six had residual deficits at 1 month after dosing.

Discussion

How many healthy volunteers have taken part in a phase 1 trial of a MAb?

Only six of the 44 trials identified from the ClinicalTrials.gov website had been published. Even when the trial results had been published, in some cases the healthy volunteer data were summarized briefly in a paper whose main purpose was to describe preliminary results in patients. Ross *et al*. [11] noted similar under-reporting of other types of trial listed on ClinicalTrials.gov: only 46% had been published. The two main reasons for non-publication of trials are probably a lack of interest on the part of both investigators and journals in publishing unremarkable results obtained in healthy volunteers and commercial confidentiality. Of course, it is possible that more than six of the 44 trials in ClinicalTrials.gov might be published in due course, so our findings may ultimately prove too pessimistic.

In addition to the 10 trials identified in the ClinicalTrials.gov website that had results reported (publications, press releases, GSK Clinical Study Register), our PubMed and Google searches yielded a further 26 publications. Taken together, those 36 involved a total of about 1700 healthy volunteers.

If we extrapolate from our finding that only one in four or so of the trials from the ClinicalTrials.gov website has been reported, the 26 trials identified via PubMed and Google imply the existence of a much larger number of

unpublished trials – about 100, say. Taking the results of all our searches into account, and estimating the publication rate at about 25%, our best guess is that, to date, there may have been about 150 phase 1 trials of MAbs in healthy subjects. The 36 published trials involved an average of about 50 subjects each, so our estimated total of 150 trials might have involved about 7500 subjects, some of whom must have received placebo. Of course, all our estimates can be criticized because they are, inevitably, speculative. However, given the number of MAbs that have been identified and developed, and the fact that some MAbs have never been given to healthy subjects, it seems reasonable to assume that the total number of healthy subjects who have participated in phase 1 trials of MAbs is probably in the range 5000–10 000, and is unlikely to be more than 20 000.

What is the safety record of phase 1 trials of MAbs in healthy volunteers?

Apart from the TGN1412 trial, the safety record of MAbs in healthy volunteers appears to be good, provided that the unpublished trials had outcomes as favourable as did the published ones.

If we take the number of healthy volunteers who have participated in phase 1 trials of MAbs to be within our estimated range of 5000–10 000 and assume that there have been no unpublished casualties, the catastrophic outcome of the TGN1412 trial implies that, to date, the risk of a life-threatening adverse effects of MAbs in such trials is about 1 in 850 to 1 in 1700 volunteer-trials. If there has been even a single unpublished casualty, our estimated risk rises to about 1 in 425 to 1 in 850 volunteer-trials. Thus, whether there have been any unpublished casualties or not, the TGN1412 disaster alone has ruined the safety record of phase 1 trials in healthy volunteers.

What is an acceptable risk to healthy volunteers?

Risk can be defined as the product of the probability of harm occurring and the magnitude of that harm when it does occur [12].

It is generally agreed that the risk of harm to a healthy volunteer in a phase 1 trial must be 'minimal', or 'negligible', because the subjects can derive no therapeutic benefit from participation [13]. 'Minimal risk' has been defined *qualitatively* in several ways, but all of them are problematic:

- 'research bears minimal risk if it is to be expected that it would result, at the most, in a very slight and temporary negative impact on the health of the person concerned' [14]. That definition is inadequate for our purposes, because it seems intentionally to exclude even a tiny risk of a severe or life-threatening adverse effect.
- 'a risk has ceased to be minimal where there is a risk that makes one stop and think' [15]. Although pithy, that definition is useless because individuals vary so greatly in the level of risk that might make them stop and think.
- 'the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests' [16]. That definition is more helpful than the preceding ones, but is still unsatisfactory because of the breadth of risks that may be 'ordinarily encountered in daily life' by different people.

If the question of what is an acceptable level of risk to healthy volunteers is to be debated sensibly and productively, it is essential first to define 'minimal' or 'negligible' risk in *quantitative* terms. Without a quantitative estimate, there is no common currency in which to exchange views about the acceptability of any given level of risk.

Risks ordinarily encountered in daily life

We take 'daily life' to include all common forms of employment, sport and recreation, travel on foot, by road vehicle, and by aircraft. Although daily life could also be taken to include risks such as exposure to environmental pollutants and radioactivity, the nature and time course of those risks differs so greatly from participation in a phase 1 trial that we have excluded them from consideration.

Comparison of the risks associated with different activities of daily life is not straightforward, because the data can be presented in several different ways. It is essential to know the number of individuals exposed to the risk, the duration of exposure (or the number of exposures), and the number of casualties. It might seem helpful to compare the risk of taking part in a phase 1 MAb trial to the risk of flying as a passenger on a commercial airliner. However, air travel is impossibly safe. The odds of being killed in a single airline flight are 1 in 29.4 million journeys [17].

Researchers in the USA have noted that, among 'everyday activities', journeys by car (automobile) pose the highest risk of death to children, with mortality up to about 4 per 1 000 000 journeys, in the age group 15–19 years. However, the risk of important morbidity was highest for participation in sports, with 58 permanent disabilities per million instances of playing basketball [18].

In England and Wales, the annual risk of a transport-related death in men aged 15–34 years is 8.2 per 100 000 population [19]. It might be supposed that many sporting activities would carry a higher risk than that, but in reality activities such as canoeing or rock climbing have average annual mortality risks as low as 1 and 3 per 1 000 000 people, respectively [20].

Even with such hair-raising pursuits as skydiving or hang gliding, the risk of death is not alarmingly high (i.e. not as high as the parents of participants believe it to be). The risk of death is 1 per 141 509 jumps and 1 per 116 000 flights, respectively [20–22]. However, there is at least one

'extreme' pastime that is alarmingly risky. 'Base jumping' carries a risk of death of 1 in 2317 jumps [23].

How safe is participation in a phase 1 trial of a small molecule?

Phase 1 trials of small molecules are generally considered to be safe enough to justify the use of healthy volunteers who cannot derive any therapeutic benefit. Ethics committees do not raise any objection in principle to the participation of healthy volunteers in FIH trials of small molecules, even though such trials are clearly not risk free. It follows, therefore, that society is willing to accept the risk associated with those trials, and that we might use that risk as a benchmark when considering the acceptability of the risk associated with MAbs.

Unfortunately, estimating the risk of phase 1 trials of small molecules is not simple, because there is no obligation to publish details of adverse events, and there is no reliable way to discover how many healthy volunteers have actually been studied. The most comprehensive review of the subject is that by Sibille and colleagues [24], who found that 15 deaths have occurred in phase 1 trials in the last 30 years in Western countries. They estimated that about 100 000 healthy subjects might have been dosed in a typical year. Of those 15 deaths, 12 either occurred on placebo or resulted from preventable drug overdose: only three deaths might have been related directly to the administration of an investigational medicinal product (IMP). Details of those three deaths are as follows:

1 A 31-year-old man had received a depot intramuscular injection of flupenthixol, 1 day before he received an intravenous infusion of a new anti-arrhythmic drug (eproxindine) which caused asystole and death [25].
2 A 19-year-old woman committed suicide (by hanging) while she was an inpatient in a phase 1 research unit, shortly after the protocol-specified, abrupt withdrawal of repeat dose treatment with the antidepressant duloxetine [26]. Although suicidal ideation and withdrawal effects of duloxetine have been reported, and young women very rarely hang themselves, the role of duloxetine withdrawal in this tragic event nevertheless remains uncertain.
3 A 24-year-old woman developed ARDS and died from multi-organ failure, after inhaling high dose hexamethonium in an exploratory, 'proof of principle' trial [27]. Although hexamethonium is an 'old' drug, the novel route and high dose mean that the drug was truly an IMP.

The data gathered by Sibille *et al*. [24] suggest that at least three IMP-related deaths have occurred in 3 million participants in phase 1 trials of small molecules, implying that the risk of death is about one volunteer per 1 000 000 exposed. The true incidence is probably slightly higher than that, because not all of the 3 million volunteers will have received active IMP. Some will have received placebo, and others will have had doses that were far too low to be capable of causing toxicity.

As regards the risk that a young healthy volunteer will experience a serious adverse event (SAE) in any given trial, the estimates of different authors extend from about 1 per 5000 up to 1 per 250 participants [24, 28–30]. The figure of 1 per 250 participants has face validity, given that it implies that a phase 1 unit that enrols and studies 1000 subjects per year could reasonably expect to encounter four SAEs. However, it is important to note that SAEs are defined in accordance with the criteria set out in the International Conference on Harmonization Good Clinical Practice (ICH GCP), and as a result are not necessarily *severe*. As far as we are aware, no reliable data are available on the incidence of severe or life-threatening adverse events in phase 1 trials.

What is an acceptable level of risk?

It is a fundamental principle that individuals are free to take whatever risks they wish to take in their leisure hours, but the risks that others impose on them, in the workplace, for example, must be regulated [31]. Participation in a phase 1 trial as a volunteer is an activity that lies somewhere between work and leisure. The volunteers are paid for their participation, but there is no contract of employment and the volunteers lack the protection afforded by employment legislation. On the other hand, it seems unlikely that many volunteers participate simply for the purpose of enjoyment. The volunteers rarely have the medical or scientific knowledge to assess the risks of taking part in a phase 1 trial, so they are dependent upon the sponsoring pharmaceutical company, the regulatory authority, the principal investigator and the ethics committee to ensure that those risks are 'negligible' or 'minimal'. As regards protection against excessive risk, therefore, the volunteer is in very much the same position as are employees in their place of work.

It is clearly impossible to define an exact level of risk that would be universally accepted, for example, clinicians and research ethics committees hold different views [32, 33]. However, it should be feasible to set a maximum risk that *most reasonable people* (i.e. people like us) would accept. Since there is a general acknowledgement that phase 1 trials of small molecules are acceptably safe and the risk of death in such trials is probably of the order of 1 per 100 000–1 000 000 volunteer-trials, we suggest that for most reasonable people the threshold of acceptability must lie within that range. Of course, we would all prefer to set the threshold of acceptability at 1 per 1 000 000 or better. However, many apparently sensible individuals indulge in leisure activities (such as skydiving or hang gliding) that carry a risk of death of about 1 per 100 000 person-expeditions, which suggests that those individuals are prepared to accept high risks in the pursuit of enjoyment. Moreover, many of us expose ourselves to a risk of death substantially greater than 1 : 100 000 per year in a

transport-related accident, in return for the enormous utility and occasional pleasures of travel. So, we take a 'negligible' or 'minimal' risk of life-threatening injury or death to be somewhere in the range 1 : 100 000–1 000 000 volunteer-trials.

Safety record of MAbs in healthy volunteers

In the TGN1412 incident, six healthy volunteers had life-threatening adverse events and two of them nearly died. If we take our rough estimate (see above) that about 5–10 000 healthy volunteers have participated in trials of MAbs, those six casualties mean that the apparent risk of life-threatening injury in such trials is about 1 : 850–1 : 1700 volunteer-trials. A risk of that order would clearly be completely unacceptable. As we have argued above, a reasonable threshold of acceptable risk is in the range 1 : 100 000–1 000 000, as in the case of phase 1 trials of small molecules. Our most optimistic estimate of risk, which is 1 per 1700, would be far higher than those of the most 'dangerous' sporting activities, including skydiving. Indeed, it would be of the same order as the risk of base jumping (1 death per 2317 jumps) [23].

Because of the extraordinary number of casualties in the TGN1412 trial, the safety record of phase 1 trials of MAbs in healthy volunteers will not approach an acceptable level until many more subjects have been dosed uneventfully with MAbs. About 600 000 further volunteers would have to be dosed to achieve a safety record of one life-threatening adverse event per 100 000 volunteer-trials. Even if there had been only one serious casualty in the TGN1412 trial, a further 100 000 volunteers would have to be dosed before the safety record of MAbs in volunteers reached an acceptable level. It is unrealistic to suppose that such large numbers of volunteers will be dosed with MAbs in the foreseeable future, so MAbs are, effectively, permanently burdened with a poor safety record.

In spite of that numerically disastrous safety record of phase 1 trials of MAbs in healthy volunteers, the consensus is that it is acceptable to continue to do such trials in healthy volunteers. Why?

First, our estimate of risk of 1 per 1700 is clearly unreliable, because the number of volunteers exposed to date (10 000, say) is far too small to assess reliably a low level of risk. Second, the near-simultaneous first administration of a novel MAb to six volunteers is a practice that will surely never be repeated. It is now usual to give the very first dose level to a single 'sentinel' subject, at least 24 h before exposing more subjects to the MAb. Third, sponsors, regulatory authorities, ethics committees and investigators are all much more cautious about MAbs than formerly, so starting doses of MAb are likely to be lower. Fourth, all the interested parties are now acutely aware of the potential of MAbs, particularly those with agonist activity and/or cellular targets, to cause SAEs such as 'cytokine storm', and 'higher risk' MAbs would not be given to healthy volunteers. Fifth, investigators are surely now more aware of the limitations of their knowledge, and are more likely to seek expert advice. Finally, helpful guidelines have been issued by the Expert Scientific Group on Phase 1 Clinical Trials [3] and by the European Medical Agency [34].

A further reason why phase 1 trials of MAb continue to be done in healthy volunteers is that there is now huge experience of the safety of single doses of MAbs in patients with the target disease. That favourable experience can be back-extrapolated to early phase trials in healthy volunteers. However, repeated dosing with many MAbs is now well-known to be capable of causing serious toxicity, such as opportunistic infection, recrudescence of latent infection, malignancy, cardiotoxicity and skin disease. So, clinical experience supports the continued use of single doses of MAbs in healthy volunteers, but generally excludes the possibility of repeat dose trials.

Conclusions

There is substantial under-reporting of phase 1 trials of MAbs in healthy volunteers, so their safety record is difficult to assess. All pharmaceutical companies should publish details of their phase 1 trials online, as recommended by the Expert Scientific Group on Phase 1 Clinical Trials [3]. The Clinical Study Register established by GSK [10] shows that such publication is both feasible and valuable.

The disastrous outcome of the TGN1412 trial means that the safety record of phase 1 trials of MAbs in healthy volunteers is doomed forever to be unacceptable. However, the medical and scientific community has evidently treated that unacceptable safety record as the result mainly of an inadequate sample size, and MAbs continue to be given to healthy volunteers. Based on the limited data that are currently available, there is adequate justification for that policy.

Most of the trials we identified would not be considered as 'high risk', because they involved antibodies that were antagonists rather than agonists, so were unlikely to cause 'cytokine storm'. The published data suggest that phase 1 trials of MAbs that are antagonists can be done safely in healthy volunteers, if the Expert Scientific Group (ESG) [3] and Committee for Medicinal Products for Human Use (CHMP) [34] guidelines are followed. The choice of healthy or patient volunteer must be made on a 'case by case' basis. Extensive risk mitigation measures must be taken in trials of MAbs that are first in class, target immune-competent cells, or are capable of inducing cytokine release.

Competing Interests

All three authors are employed by Hammersmith Medicines Research (HMR), which does first-in-human trials of MAbs. SW is a director of HMR.

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