Background

On Monday 13 March 2006, six volunteers taking part in a phase I clinical trial of a monoclonal antibody, TGN1412, experienced severe adverse events. The trial was sponsored by TeGenero and took place at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London. This was the first human trial of TGN1412, an immunomodulatory humanised agonistic anti-CD28 monoclonal antibody that was being developed for the treatment of autoimmune and immunodeficiency diseases.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has launched a full inquiry into events. Whilst the MHRA investigations continue, access to full information about the trial is limited. As part of the Academy of Medical Sciences' on-going work into the research and development of new medicines, which included the publication of 'Safer Medicines' in November 2005[1], a small working group was convened to discuss some of the broad questions and issues arising from the TGN1412 trial. A list of working group members is annexed.

The working group's remit was to:

- Consider the potential role of antibody therapies as treatments;
- Identify potential safety hazards unique to the assessment of antibody therapies;
- Provide a framework for further steps to ensure the safe introduction of new antibody therapies.

The working group's discussions addressed four broad areas:

1. The importance of antibody therapies
2. The potential risks associated with antibody therapies
3. Special testing and regulatory considerations for antibody therapies
4. Sources of clinical information on adverse effects associated with antibody therapies

1. The importance of antibody therapies

The importance of antibody therapies in treating human disease is significant. Over twenty antibodies have been approved for human therapy or are in late stage clinical trials in the US and Europe and hundreds more are in pre-clinical development. It is difficult to estimate the number of patients who have benefited from antibody therapy worldwide, but the figure certainly exceeds 1 million. Antibody treatments represent key therapeutic advances in the treatment of rheumatoid arthritis, cancer and gastrointestinal disorders, amongst others.

Most monoclonal antibodies are designed to work in one of three ways: by recruiting components of the immune system to kill cells (usually cancer cells); by delivering a diagnostic or therapeutic payload such as a radionuclide or drug; or by acting as blocking agents through binding to target molecules in body fluids or on the surface of cells to inhibit immune and inflammatory reactions that can

[1] http://www.acmedsci.ac.uk/images/publication/SaferMed.pdf

cause damage to the host. The rationale behind TGN1412 differs in that it is a 'superagonistic' antibody designed to activate and expand the pool of a subset of immune cells (T_{REG} cells).[2]

T_{REG} cells play a crucial role in the control of immune responses to self-antigens. It has been postulated that an imbalance between numbers of T_{REG} cells and autoreactive T cells (T_{CONV}) may be involved in several autoimmune disorders. Specifically, reduced numbers or impaired function of T_{REG} cells have been linked to type 1 diabetes, multiple sclerosis and rheumatoid arthritis. Furthermore, T_{REG} cells have been shown to be involved in the regulation of immune responses against infectious pathogens, thus ensuring an appropriate response with minimum pathology. T_{REG} cells can also control immune responses to allergens and so prevent diseases such as asthma.

Thus, drugs that can expand the pool of T_{REG} cells and enhance their suppressive activity are being investigated as important therapeutic tools. When designing such a tool, it is important to ensure activation and/or expansion of only T_{REG} cells, without activation of other immune/inflammatory cells that may cause damage. While most antibody therapies exhibit an antagonistic function, antibodies that activate immune processes (i.e. agonists) may therefore present specific additional safety issues that need to be considered in pre-clinical and clinical testing.

2. The potential risks associated with antibody therapies

Antibody therapies present several issues for safety and efficacy testing that differ from conventional 'small molecule' drugs. The most important of these relate to the specificity of antibody action and the relative youth of this research field, which means there is a smaller body of knowledge to draw on when attempting to predict unwanted effects.

Antibodies have multiple functions incorporated into a single molecule. Variable regions of the antibody mediate target specificity while constant regions mediate effector functions including Antibody Dependent Cell-mediated Cytotoxicity (ADCC) activation, complement activation and facilitation or persistence of antibody in the blood. The constant regions also provide a framework to link multiple variable regions so that target molecules can be cross-linked. The combination of selective target binding with effector functions can elicit potent therapeutic actions, but care must be taken that the effector functions are not activated where they may cause toxicity. Recombinant DNA technology makes it possible to create antibody-based pharmaceuticals in which only the desired effector functions operate.

Each antibody expresses a different binding site that allows it to bind to different targets, or to the same target with different affinity. The highly specific nature of antibody binding is key to therapeutic success but also presents unique problems in assessing toxicity. It is crucial to establish whether an antibody has 'on target' actions in the animal model used for pre-clinical toxicity testing. This requires

[2] T cells require two signals to become activated: the first signal arises from an interaction between T cell receptor (TCR) molecules and peptide/major histocompatability complexes on antigen presenting cells; the second signal involves a costimulatory receptor, such as CD28. TGN1412 represents a sub-class of CD28 specific antibodies, the CD28 'superagonists', which can activate T cells, without additional stimulation of the T cell receptor. Evidence suggested that this type of agent preferentially expanded populations of T_{REG} cells over T_{CONV} cells. See Beyersdorf N *et al* (2005) 'Superagonistic anti-CD28 antibodies: potent activators of regulatory T cells for the therapy of autoimmune diseases' *Ann. Rheum. Dis*. **64**: iv91-iv95.

special consideration in relation to species choice and may necessitate the generation of novel genetically modified animal models or of bespoke antibodies for the animal protein. In addition, in many animal models the antibody may not bind to the target protein with the same degree of affinity as it would bind to the human protein. The antibody may therefore elicit a considerably lesser, or different, effect in the animal model than in humans.

The distribution of the molecular target on a wide variety of cells and tissues can raise unexpected biological effects and consequent toxicities that are not anticipated by pre-clinical experiments focussing on a particular biological reaction. A further risk therefore results from the unexpected expression of the target on other cell types or tissues, or from an unexpected biological activity of the target.

Differences in the ways in which antibodies interact with the innate immune mechanisms of animals and humans must also be taken into account when interpreting toxicity results. Antibodies differ in their Fc regions, which permit binding to different Fc receptors on innate immune cells and so activate a cascade of effector mechanisms in the vicinity of the therapeutic target. Some Fc regions can also bind and activate a set of plasma proteins; the 'complement' system. It has been argued that, if the therapeutic intent is to block function or provide agonist activity, it may be advisable to specifically mutate the Fc region, so that the antibody is unable to activate cells of the innate immune system, as well human complement.

Therapeutic antibodies are large proteins capable of eliciting immune responses against themselves, i.e. they can exhibit immungenicity. Such responses may interfere with the therapeutic effect of the antibody and may cause hypersensitivity reactions.

The high affinity of antibodies for their targets means that target receptors can become saturated, even at very small concentrations. Unlike conventional 'small molecule' compounds, antibodies therefore rarely show a linear dose-response effect. Antibody affinity can also affect whether antibodies bind univalently or bivalently to their target. Dose effects can be further complicated by spontaneous dimerisation of the antibody. Understanding the biological mechanism of antibody action is an important part of developing a potential drug and detailed expression studies of the antibody in humans provide important information.

These factors, together with the smaller body of antibody therapy research knowledge, increase the uncertainty around the likelihood of unwanted effects when the drug is used in humans. Progress of all antibody therapies to the phase I, 'first in man' stage of clinical trials should therefore proceed with caution. Furthermore, agonist antibodies, which represent a novel antibody action, must be approached with extra caution. Regulators will need to consider carefully whether 'on-target' effects have been demonstrated in the species used for toxicity testing.

3. Special testing and regulatory considerations for antibody therapies

Most importantly, the potential risks of antibody therapies mean that the appropriate regulatory authorities should be involved in on-going and iterative dialogue with researchers throughout the drug development process. It may also be necessary to enrol specialist consultants or advisors during the development of the biologic. The UK MHRA has an Expert Advisory Group on Biologicals that meets monthly and reports to its Commission on Human Medicines (CHM). The US Food and Drug Administration (FDA), also has a separate committee dedicated

to regulating biological medicines, the Centre for Biologicals Evaluation and Research (CBER). The European Medicines Agency's (EMEA) Biologics Working Party is also in the process of revising its guidelines on production and quality control of monoclonal antibodies. An essential factor in the development of an antibody therapy is transparency; widespread awareness and discussion of all stages of development, particularly phase I studies, provide an important check on progress.

During development, when antibodies are first administered to healthy volunteers, the intent is to use dosing so low as to elicit no (therapeutic) effect. At this stage, biomarkers are often used to monitor any physiological changes. Healthy volunteers may be used, instead of patients, because generally toxic effects would not be likely at the very low doses used. It would be usual practice to administer a single dose in a single patient, who would then be observed for an appropriate period of time. In many instances, volunteers are first given a 'test dose', of a small fraction of the trial dose, before the full dose is administered after a short period (typically less than one hour). It is important to recognise that, during this crucial step of 'first into man', the assessment of antibody toxicity is likely to be less precise than for conventional small molecule drugs. Whatever the protocol for a new antibody therapy, the choice of starting dose is crucial and the design of the initial clinical study must be such that the degree of uncertainty is appropriately taken into account.

Antibody therapies directed at the immune system may have complex effects, both predictable and unpredictable. Their clinical evaluation should include analysis of the predicable effects at the cellular and molecular levels, as well as prior consideration of possible unpredictable effects to enable appropriate sampling and testing within the trial.

The relative youth of research into antibody therapies presents important ethical considerations, particularly around the involvement of healthy volunteers where the risk/benefit ratio differs from that associated with patients. Ethical review of novel antibody therapies is a critical process, which may involve both the ethical committee of the company developing the drug and the NHS research ethics committee (REC) associated with the hospital in which the trial is conducted. The input of specialist scientific advice to inform ethical review is a key consideration and investigators should provide as much information as possible to ethics committees.

Clinical trial participants should always be fully informed of the level of risk involved and the degree of uncertainty. Where appropriate, gaining consent from trial participants should involve a 'cool-off' period between provision of trial information and giving consent, and/or attendance by a friend or relative of the trial subject. Financial inducements to take part in trials should be considered carefully by the relevant ethics committees and regulators.

4. Sources of clinical information on adverse effects associated with antibody therapies

Clinical trials of small molecule compounds have a lengthy history and clinicians have established mechanisms for obtaining information in the rare instance of adverse effects. Due to its relative youth, this mechanism is not so well established for antibody therapies and there appears to be a reliance on personal and professional contacts. The treatment of adverse effects, and where to obtain advice, should always be part of the risk assessment of a trial protocol. However, intensive care staff, who may have no involvement in the trial, may benefit from a more formal mechanism for obtaining such information.

In addition to a central source of data on adverse effects, a central repository of information about the treatment of adverse effects of antibody therapies, ideally international and backed up by a national expert panel available for telephone consultation, should be considered. Given the rarity of adverse events, such a facility would allow benchmarks of best treatment and clinical management to be established and disseminated as quickly as possible. There is already extensive UK experience in the clinical evaluation and therapeutic use of antibody therapies, particularly in the fields of autoimmunity, oncology and transplantation.

The future

Antibody treatments have already provided huge benefit to patients and it would be unfortunate if events related to the TGN1412 clinical trial were to hinder or stop research into other promising antibody therapies. However, the points raised in this paper illustrate the special risks associated with novel antibody therapies and the subsequent regulatory considerations that must be taken into account, particularly the use of existing knowledge to identify and minimise potential risks. The lessons of TGN1412 must be applied to strengthen the framework in which such research is conducted. Regulations governing the development of new medicines, which focus on more conventional, small molecule compounds, must be adapted appropriately to the new wave of biological medicines. The Academy of Medical Sciences will play an on-going role in providing expert comment and advice on how the lessons learnt should be incorporated into research and development practice.

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5 April 2006

Annex: Working group membership

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Professor Richard Begent FMedSci
Professor of Clinical Oncology, Royal Free & University College Medical School

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Relevant interests of the working group are available on the Academy's website www.acmedsci.ac.uk

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