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Assessing the risk of handling monoclonal antibodies

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We read with interest the paper by Langford et al on assessing the risks of occupational exposure to monoclonal antibodies (MABs) (*Hospital Pharmacist* 2008;15:60–3).

It adopts the principle enshrined in guidance on this subject dating back to at least 2001, that the two main areas of risk are the immunogenicity of the exogenous antibodies and the biological consequences of antibodies combining with their target antigens. It then attempts to quantify these two areas of risk for a variety of therapeutic antibodies in clinical use and produce an overall risk score. Based on this score, the authors provide guidance on whether the antibody can be manipulated in clinical areas or should be handled in pharmaceutical isolation facilities. We are concerned that their scoring system is likely to produce misleading estimates of risk.

Although the authors are correct in their assertion that the immunogenicity of MABs falls with the decreasing proportion of the molecule that is of murine origin, it is far from clear that the development of human-antichimera antibodies (HACAs) is of major significance. For example, when rituximab is used intravenously for the treatment of lymphomas, a HACA development rate of 1.1 per cent has been reported.¹ However, HACAs appear to have little impact on the tolerability or efficacy of rituximab² in this setting. Furthermore, although Roche estimates that in excess of 1.3 million doses of

rituximab have been administered over the last decade, we are unaware of any reports of sensitisation among those occupationally exposed to this or any other antibody produced by the company.

We are more concerned however, about the scores applied by the authors to reflect their interpretation of the specific toxicity of individual antibodies. They have taken safety hazards identified in patients receiving therapeutic doses and applied these to staff who will, at worst, absorb doses several orders of magnitude lower than those experienced by patients. At these doses it is unfeasible that they will noticeably perturb normal physiologic processes in the way suggested.

Using rituximab as an example, they have assigned this to risk level 3 (on a 4 point scale) because of “significant toxicity”. Although the nature of this toxicity is not specified, it is likely to refer to infusion reactions, including severe cytokine release syndrome, which are the consequence of massive tumour lysis in patients with B-cell malignancies. First-dose infusion reactions are 10-fold less common in rheumatoid arthritis patients than in those with lymphoma.¹

Occupational levels of rituximab are likely to produce, at worst, minute levels of cell kill in healthy individuals and it is unfeasible that such individuals will suffer significant harm as a result of the combination of rituximab with the CD20 antigen it recognises. Similar comments could be applied to most of the “significant toxicities” listed by the authors in Table 1 of their paper.

Three possible exceptions are gemtuzumab (presumably the ozogamicin conjugate), ibritumomab tiuxetan and tositumomab, since these are actually conjugates of MABs with cytotoxic drugs or radionuclides. In these cases, it is not the antibody that causes concern but the conjugated effector molecule, since a single molecule of such an agent, capable of damaging DNA, could, theoretically, be carcinogenic or mutagenic. The radioactive or cytotoxic nature of these conjugates would already dictate that they be handled in a protective environment.

The authors appear to have had their views on the safety of MABs shaped, in part, by recent events during the phase I trial of TGN1412. Although this trial raises some questions about the conduct of early-phase clinical trials, its relevance to occupational exposure to marketed products seems tenuous. TGN1412 was not and is now unlikely ever to be licensed because of its toxicity and yet, despite the consequences to the study

volunteers, we are unaware of the staff involved in the study suffering any adverse effects.

We believe that, to be practically helpful, any risk rating scheme needs to take into account the likely consequences of exposure to those systemic levels of antibodies likely to be experienced by healthcare professionals. At present, we feel that the assessment carried out by Langford et al has overestimated the hazards associated with a group of drugs which have already been used widely for over a decade with no evidence of harm to those preparing or administering them.

Although overestimating the occupational risk of handling a new class of drugs may look like admirable caution, it does have a downside. We are still a long way from fulfilling the vision of the Breckenridge report³, where all intravenous drugs would be prepared centrally. Hospitals are currently forced to prioritise products for pharmacy versus clinic or ward-based preparation. Any system that exaggerates the risk of low-hazard products may result in these being prepared centrally and displacing those whose preparation represents a greater risk to patients.

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2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treatment Reviews* 2005;31: 456–73.
3. Breckenridge A. Report of the working party on the addition of drugs to intravenous infusion fluids. London: Department of Health and Social Security; 1976.

STEPHEN LANGFORD, principal pharmacist (technical services) at University Hospitals Birmingham and SEAN FRADGLEY, senior pharmacist (quality control) at University Hospital of North Staffordshire respond:

We thank Roche for their letter in response to our paper on assessing the risks of handling monoclonal antibodies. Our

Letters to the editor

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paper reflects two underlying issues confronting healthcare staff. First, given the precedence of safety concerns about cytotoxic medicines, questions regarding MABs need to be asked. Second, information on the underlying science behind the mode of action(s) of MABs and their potential risks has not been readily assessable in information sources to healthcare staff. Moreover, while guidance from 2001 has identified the likely risk area (that of immunogenicity), no indication of the underlying data needed for assessing risks has been given.

We agree that the significance of antibodies, particularly to humanised MABs is unclear; particularly since the immunogenicity appears to involve binding, not neutralising, antibodies and may not be "memorised" within the immune system. However, we must make the point that potential exposure of healthcare staff is of a chronic long term nature to multiple agents, and they are not being subjected to surveillance measures designed to detect potential adverse effects.

The risk scoring system adopted in our paper is a relative one and it is difficult to see what criteria, other than relative capacity to produce an immune reaction and known severity of associated therapeutic toxicities, could be used. We accept that further refinement of such an approach must take into

account whether the toxicities are specific in a response to the treatment of a disease state (eg, tumour lysis syndrome), and toxicities arising from the intrinsic reaction of a MAB with its target antigen, which may be present

in healthy staff. MABs do have intrinsic potential for toxic effects (eg, complement-mediated cytotoxicity, profoundly immunosuppressive responses, skin toxicities from MABs which target epidermal growth factor), therefore the issue is the extrapolation of risk based on the use of therapeutic doses, as we acknowledged in our paper.

Clearly, a view may be taken that the likely exposure level of healthcare staff will be insignificant, particularly if the simple precautions of wearing gloves and face masks are taken when handling MABs.

In regard to TGN1412, it was both the potential release of cytokines as a potential toxicity of some MABs and the reference to lung-mediated toxicity that caught our attention. This was an isolated event, as Mr Summerhayes and Mr Cole state. However, it drew attention to the fact that the most likely exposure route for healthcare staff is via the inhalation of aerosols arising from the preparation and administration of injections. Moreover, research is being carried out into the possibility of the therapeutic administration of protein products via the lung (though probably not complete MABs).

We welcome the letter from Roche in assisting healthcare staff gain a balanced understanding of the issues in handling MABs.

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