Anticipating, Recognizing, and Preventing Hazards Associated with \textit{in Vivo} Use of Monoclonal Antibodies: Special Considerations Related to Human Anti-Mouse Antibodies

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Abstract

The advent of monoclonal antibodies offers abundant potential benefits to diagnosis and therapy of many conditions. However, with widespread use come greater concerns regarding possible side effects and complications.

Antibodies, including monoclonals, react with antigens which may be represented on tissues other than those to which they were raised. Although histochemical surveys of tissues may be performed, these may not necessarily be predictive of \textit{in vivo} cross-reactivities. This consideration mandates carefully performed preclinical toxicological studies prior to use in humans.

For murine monoclonal antibodies, the type most commonly available, issues related to potential immunogenicity are of paramount concern. Very little substantive information has accrued regarding the prevalence of these antibodies in the general population, the mechanism by which these antibodies are elicited, or the predictive value of assays for their detection. This knowledge is crucial for the development of strategies for blunting or controlling the human anti-mouse antibody response. Contaminants in manufactured monoclonals also pose inherent danger to recipients. Among those commonly encountered are microbes, DNA, and manufacturing reagents (e.g., sera, column components, and tissue culture additives). Strict adherence to proper manufacturing technique usually will minimize these concerns. However, in the absence of well-defined cause/effect relationships between toxicity (theoretical or real) and agent, complacency that a given product is safe is ill-advised.

The Food and Drug Administration has disseminated a compilation of concerns and suggestions for addressing them in the document “Points to consider in the manufacture and testing of monoclonal antibody products for human use.” The precepts outlined in that document and a close working relationship between manufacturers of monoclonal products and scientifically astute regulators together represent an effective approach to minimizing the risks of monoclonal therapy in diverse patient populations.

Theoretical as well as technical and practical questions need to be overcome before monoclonal antibody therapy achieves the clinical promise inherent in the availability of unlimited quantities of pure, ultraspécific immunoglobulin. As these barriers fall to the innovations of modern biotechnology, new considerations related to the consequences of their widespread use arise.

Three major sources of problems potentially associated with monoclonal antibody administration exist: impurities associated with preparation or manufacture; inherent properties of the immunoglobulin molecule; and the host response to protein.

Impurities may arise as a result of methods used to propagate the hybridoma line. The most notable concerns thus far have been viruses or DNA contamination. Obviously any component added to enhance growth or yield has the potential for unexpected effects. The use of chromatography columns and separation reagents (i.e., Staph protein A) raises possibilities of leaching of unwanted and potentially toxic compounds into the product. Furthermore, chelates and conjugates such as radio- nuclides, toxins, and antineoplastic drugs carry their own special side effects.

Approaches to minimizing theoretical or practical consequences of these have been outlined in the FDA’s “Points to consider in the manufacture and testing of monoclonal antibody products for human use.” This document relates to monoclonals and a companion document describes corollary procedures relating to cell substrate issues. These documents have been widely disseminated and are available from our Center through the Freedom of Information office (301-496-9508). In addition, a number of articles have appeared either in monographs (1) or in reports of symposia where representatives of the FDA have attended (2, 3).

Issues related to the antibody molecule per se may be conceptualized in relation to its immunological domains. The Fc fragment conveys the capacity to react with certain tissue receptors, particularly if the antibody molecules have been aggregated. The consequences of immune complexes and the characteristics of their pathophysiology have been described in detail elsewhere (4). The Fab portion, or antigenic combining site, reacts with structures identical to the original immunogen, or in some cases, related ones. The potential for unexpected cross-reactivities carries with it the possibilities for unanticipated effects. This situation may be particularly magnified in cases where the antibody is conjugated with a toxic substance. Thus far, the best defense against these potential complications has been optimal knowledge of the immunogen and its chemical structure, extensive testing for cross-reactivity \textit{in vitro}, and preclinical studies aimed at determining organ-related toxicity.

The major unknown with possibly critical implications for monoclonal antibody administration is the potential development of immune responses against the foreign protein (in most cases, mouse antibody). The development of anti-antibody responses conceivably could inhibit or neutralize the antibody or impair its therapeutic effects. At the same time, the immune response could take the form of an allergic reaction with consequences which could outweigh any beneficial effects.

Relatively little information regarding human anti-mouse antibody responses has been codified. Many reports describing attempts at therapy using monoclonals contain sections which deal with this issue, but only recently have articles appeared, the main thrust of which is an analysis of this response (5). The authors whose contributions follow this summary have been among the leaders in advancing cogent knowledge in this area. Their papers deal with the incidence of antibody responses to certain antineoplastic monoclonals (mainly anti-colon carcinoma) and describe appropriate methods for detecting differing class and subclass responses, as well as determining the incidence of antidiotypic responses as opposed to those against framework structures (6).

Other important issues in this area may be outlined as fol-

1 Presented at the “Second Conference on Radioimmunodetection and Radioimmunotherapy of Cancer,” September 8–10, 1988, Princeton, NJ.

2 The abbreviations used are: FDA, Food and Drug Administration; HAMA, human anti-mouse antibody.
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allows. What is the incidence of the response, and how is it determined by dose, route of administration, and isotype of the immunogen? What are the optimal methods for assay of anti-mouse antibody responses, and are there differences between antibodies detected in one or another assay procedure? Are there any true predictors (level of anti-antibody, skin test, small dose challenge) of allergic responses? Are strategies for diminishing HAMA (immunosuppressive drugs, reticuloendothelial blockade, lymphokine administration, plasmapheresis, or ex vivo column absorption) necessary and are they effective clinically? How does the presence of HAMA impede the efficacy of the antibody or may it in some cases augment a desired effect?

These and related issues, have been the subject of a recent (December 26-27, 1988) symposium sponsored by the FDA. This conference represents an important first step in establishing common ground for scientific study of this problem, for establishing standard procedures for detecting the response, and for understanding the implications of the presence of HAMA. The proceedings are currently being prepared for dissemination and may be ordered from the Division of Investigational New Drugs, Office of Biologies Research and Review (301-493-4864).

References

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