Biologics in the Pipeline: Large Molecules With High Hopes or Bigger Risks?

Honghui Zhou


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What is This?
Today, more than ever, big pharmaceutical companies are venturing into the biotechnology arena with the hope that novel therapeutic biologics will fundamentally reshape the pharmaceutical landscape. Several companies are even projecting optimistically that, within the decade, therapeutic biologics will comprise a majority of their commercial portfolios.

Therapeutic biologics derived from proteins are generally thought to be less prone to untoward effects than small molecular entities derived from chemical synthesis. Although this may often hold true for certain targeted biologics, this may not be the case for all biologics. The recent unexpected outcome of the first-in-human (FIH) study of TGN1412 clearly indicates the need for extra precaution whenever an investigational product is first evaluated in humans—but perhaps even more so during initial clinical investigation of monoclonal antibodies (mAbs) designed as agonists.

In the TGN1412 FIH study, for example, this superagonist anti-CD28 mAb was rapidly administered intravenously (ie, the infusion lasted 3 to 6 minutes) to 6 healthy volunteers in short sequence (ie, 10 minutes apart). Even though the selected FIH dose was only 1/500th of the reported safe animal dose, all 6 volunteers experienced an acute, immune-mediated cytokine storm that unfortunately led to multiorgan failure. The Medicines and Healthcare Products Regulatory Agency (MHRA), in conjunction with the German Regulatory Authorities, subsequently conducted a series of inquiries and inspections. Their final report recently concluded that the tragic events were not the result of any errors in TGN1412 manufacturing, formulation, dilution, or administration.

An independent Expert Scientific Group (ESG) appointed by the Secretary of State for Health in the United Kingdom, however, determined that—although the animal safety and toxicology studies of TGN1412 adequately fulfilled the requisite regulatory requirements—the overall preclinical program did not adequately predict a safe FIH dose. The ESG then listed 22 specific recommendations for ensuring the safety of future FIH study participants. These recommendations particularly addressed methods of determining safe starting doses in humans as well as selecting appropriate observation time periods between sequential dose administrations in early phase I studies.

The serious adverse events that occurred during the TGN1412 FIH study were, in hindsight, not altogether surprising considering the inherent properties of therapeutic biologics. That is, because therapeutic mAbs are purposefully engineered to show high affinities for specific human protein targets, these mAbs may show little or no binding to the homologous animal counterparts. By contrast, classic small-molecule drugs are often more likely to show similar potencies in animals and humans. Consequently, Hansen and Leslie recommended that future preclinical studies of antibody-based biologics “should also include comparative measurements of the binding affinities for both human antigen and primate antigen, to control for unforeseen variations in protein structure.”

The TGN1412 incident will likely have an industry-wide effect on future development strategies of novel biologic therapies. The more cautious stepwise approach that is commonly used to develop small molecular drugs, for example, might actually be safer and just as useful in the development of large molecular biologics. At the very least, stricter scrutiny of the transition from preclinical to FIH studies of therapeutic biologics is expected from institutional review boards, patient advocacy groups, and worldwide regulatory authorities alike.

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From Pharmacokinetics, Modeling & Simulation, Clinical Pharmacology & Experimental Medicine, Centocor Research & Development, Malvern, Pennsylvania. Address for correspondence: Honghui Zhou, PhD, FCP, Pharmacokinetics, Modeling & Simulation, Clinical Pharmacology & Experimental Medicine, Centocor Research & Development, 200 Great Valley Parkway, Malvern, PA 19355; e-mail: hzhou2@cntus.jnj.com. DOI: 10.1177/0091270006297230
Other issues associated with the development of novel therapeutic biologics will undoubtedly surface as experience continues to accumulate in the clinic. Topics of particular interest include the changes happening in the regulatory paradigm, controversies surrounding marketing approvals for biogenerics, and anticipated outcomes of technological collaborations among members of the biopharmaceutical industry, academic universities, and regulatory agencies.

SHIFT IN THE REGULATORY PARADIGM

In June 2003, the Food and Drug Administration (FDA) began transferring certain product oversight responsibilities from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). The FDA believes that this restructuring will allow for a more efficient and consistent review process. Because of this regulatory paradigm shift, the following therapeutic biologic products are now under the CDER’s jurisdiction:

- mAbs for in vivo use;
- cytokines, growth factors, enzymes, immunomodulators, and thrombolytics;
- proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and
- other nonvaccine therapeutic immunotherapies.

Although the overall impact of this paradigm shift has yet to be seen, a review of the Summary Basis of Approval documents for several new biologics offers some hints. For example, during clinical development of some newer therapeutic biologics, it appears that significantly fewer clinical pharmacology studies were performed than is typically required during the development of small-molecule drugs. Furthermore, it also appears that some clinical pharmacology studies were essentially substituted with certain nonclinical studies and/or in vitro tests instead. A former CBER supervisor and clinical reviewer, on the other hand, recently forecasted that more rigorous and resource-intensive requirements would most likely be imposed during the development of biologics under CDER’s traditionally conservative watch in the future.

Another effect of the shift from CBER to CDER has to do with FDA guidance documents—particularly those pertaining to clinical pharmacology. Currently, most of the published FDA guidance documents focus mainly on issues related to investigational small-molecule drugs rather than therapeutic biologics. Regulatory guidance originally developed for small molecular entities, however, may not always be readily applied to complex therapeutic biologics. Thus, more pertinent guidance on issues specifically related to the development of therapeutic biologics would undoubtedly improve the design of an overall clinical pharmacologic program.

BIOGENERICS DEBATE

On April 12, 2006, European marketing authorization was received for the first biosimilar copy of recombinant human growth hormone. This approval followed a prolonged evaluation process that included an initial rejection by the commission, despite a positive recommendation from the European Medicines Agency (EMEA) and an eventual lawsuit against the European Commission. Less than 2 weeks later, on April 24, 2006, the European Commission granted marketing approval to another pharmaceutical company for its biosimilar copy of recombinant human growth hormone. Approximately 1 month later, on May 30, 2006, the FDA approved recombinant somatropin for marketing in the United States.

These regulatory actions were closely watched throughout the industry, where the role of generic versions of complex therapeutic biologics has generated much debate. In addition to the unclear regulatory process for biogenerics, issues surrounding their complicated production requirements, undetermined commercial viability, and the suspected volume of data needed to prove biosimilarity have also been debated since these recent approvals. Improved access to more affordable prescription drugs nevertheless remains an undisputed goal. Generic versions of complex therapeutic biologics, however, may not be expected to substantially contribute to this effort any time soon.

OPTIMIZATION OF DEVELOPMENT STRATEGIES

In contrast to conventional development programs of small-molecule drugs, development programs for therapeutic biologics have yet to receive the same corporate focus and resources across many major pharmaceutical companies. This is likely to change soon, however, as the percentage of therapeutic biologics in a typical research and development portfolio is progressively increasing. Consequently, many clinical development scientists (including clinical
pharmacologists) who have acquired expert-level knowledge and experience with small-molecule drugs are being assigned (or will likely be assigned) to therapeutic biologic development projects. This healthy influx of small-molecule drug development expertise will certainly help optimize clinical pharmacologic strategies for novel therapeutic biologics. Furthermore, this combination of clinical knowledge, practical experience, and additional resources will undoubtedly contribute to the determination of optimal dosage regimens and improve the quality of prescribing/labeling information for safer and more effective biologic therapies.

Development strategies of novel biologics will also soon benefit from better collaboration among industry, government, and academia. For example, a new coalition between the Pharmaceutical Research and Manufacturers of America (PhRMA) and several federal agencies (ie, FDA, the Foundation for the National Institutes of Health, the Center for Medicaid and Medicare Services, and the National Institutes of Health) has recently been formed to search for and validate new biomarkers. Collective efforts from this unique Biomarkers Consortium are widely expected to contribute to a shorter drug development cycle and could potentially help lower product development costs over time.

YOUR PARTICIPATION IS ESSENTIAL

In recent years, more and more therapeutic biologic candidates have poured into drug development pipelines. The clinical pharmacology strategy for therapeutic biologics has become increasingly important in drug development and presents many unique challenges. Thus, the Journal of Clinical Pharmacology has recently added a dedicated Biologics section to facilitate the sharing of novel ideas in clinical drug development, the presentation of clinical pharmacologic data, and the discussion of current topics.

The Biologics section encourages submission of manuscripts that may encompass the following areas:

- Allometric scaling prediction of clinical doses for an FIH study
- Pharmacokinetic and pharmacodynamic characteristics
- Population pharmacokinetic/pharmacodynamic modeling and simulation
- Exposure-response relationship exploration and utility
- Drug-drug interaction assessments
- Biocomparability, bioequivalence, and biosimilarity evaluations
- Biogenerics issues
- Novel formulations or delivery systems
- Therapeutic devices development
- Pharmacogenetics/pharmacogenomics applications
- Drug development strategies
- Bridging strategies
- Regulatory or PhRMA perspectives

The Biologics section strives to cultivate excellence in this new but very promising field. Clinical pharmacologists in industry, academia, and regulatory agencies are encouraged to share their innovative ideas and experiences in optimizing clinical development of therapeutic biologics. Research papers, review articles, and critical commentaries are all welcome.

We invite you to submit manuscripts relevant to Biologics subject areas directly to the Journal of Clinical Pharmacology via its online submission portal at www.rapidreview.com, with a notation in the cover letter that the paper should be considered for the Biologics section.

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Honghui Zhou, PhD, FCP
Section Editor, Biologics

REFERENCES