ELSEVIER

Analysis of therapeutic drug postmarketing megadata, coupled with regulatory monitoring, can improve patient safety and advancement of science, and decrease healthcare costs.

Channeling postmarketing patient data into pharmaceutical regulatory systems

Maria D.F.S. Barbosa[1] and David D. Smith[2]

[1] CA Consultants, PO Box 3237, Princeton, NJ 08543, USA
[2] City of Hope National Cancer Center, Department of Biostatistics, 1500 E. Duarte Road, Duarte, CA 91010, USA

A limited amount of data is typically available to support product license applications. That is further complicated by the need to make some medicines available to patients at key times, using expedited drug approval pathways. In addition, increasing immunogenicity concerns have been paralleled by a myriad of biotherapeutics entering development and/or receiving regulatory approval. Postmarketing patient safety is intrinsically dependent on the correct balance of economics, regulatory oversight and legal and enforcement issues. Here, we discuss the changing landscape of pharmacovigilance, with special emphasis on postmarketing commitments and requirements, megadata analysis, regulatory responsibilities and research opportunities. Challenges and possibilities are illustrated with therapeutic drugs approved for treatment of autoimmune diseases, diabetes, cancer, rare diseases and the resurgence of gene therapy.

Introduction

Therapeutic drug classes encompass natural products, small molecule drugs, peptides, therapeutic proteins (biotherapeutics) and small-molecule–biotherapeutic conjugates [1–5]. Most approved therapeutic drugs are either small molecules or biotherapeutics [6], and the focus on the latter has significantly increased in recent years. The overall paths for postmarketing surveillance and mechanisms for drug evaluation that will be explored in this review can be applied to all therapeutic drug classes. However, therapeutic proteins present some unique challenges related to immunogenicity that will be more closely scrutinized.

Marketed biotherapeutics can comprise reference products, biosimilars and biobetters [7,8]. A biosimilar can be defined as a biotherapeutic similar to another one already marketed for which the patent has expired (the reference product). Biobetters are improved, newer versions of reference products [9,10], and can represent a means for companies to address competition from biosimilars and maintain a market advantage after expiration of their patents. Biosimilars and biobetters have also been referred to as 'follow-on protein products' and 'second-generation products', respectively [2].

Corresponding author:. Barbosa, Maria D.F.S. (mbarbosa@cacobio.com)

Dr Barbosa
has effectively performed at all stages of drug development: preclinical, clinical and postmarketing. She has also successfully planned, directed and accelerated significant discovery of biotherapeutics and small molecule drugs with a wide range of targets. Following graduation from the PhD program at the University of Guelph, Canada, she conducted postdoctoral studies at the University of Florida, USA. She subsequently acquired broad-based experience at large pharmaceutical and biotech companies. Previous employers include Bristol-Myers Squibb, Xencor, Dupont Pharmaceuticals and CuraGen. She intermittently manages CA Consultants (http://www.cacobio.com). She is an inventor and holder of patents, as well as an author of numerous peer-reviewed papers.

Dr Smith
is a professor and co-director of Biostatistics at City of Hope. He served as a biostatistical reviewer for the FDA's Division of Oncology Drug Products for three years. After leaving the FDA, he joined the research faculty at City of Hope. Dr Smith has been a co-investigator on grants from the NCI, NIH, the American Cancer Society, the Susan G. Komen Breast Cancer Foundation and the Leukemia-Lymphoma Society. He serves on the board of directors at Pharmacyclics, and he is an author of over 80 papers in peer-reviewed biostatistics, oncology, surgery, radiation and immunology journals.

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GLOSSARY

Anti-drug antibody (ADA) Antibody generated as an immune response to a therapeutic drug.
Adverse event (AE) Any undesirable experience (i.e. a bad side-effect) associated with the use of a medical product in a patient.
Biobetter Newer and presumably improved version of a marketed biotherapeutic.
Biosimilar Biotherapeutic similar to another one already marketed for which the patent has expired (the reference product).
Biotherapeutic Therapeutic protein (biologic drug).
Distributed analysis An analysis that is distributed across multiple computers simultaneously; following the parallel computations, the results are combined centrally.
EMA European Medicines Agency.
FDA U.S. Food and Drug Administration.
Generics or generic drugs Therapeutic drugs (after patent expiry) within an equivalent reference range to the reference product and that can be used interchangeably.
Genetic epidemiology The study of how genetics and environmental factors influence the etiology of diseases.
HLA Human leukocyte antigen.
Hypersensitivity An inordinately strong immune response deleterious to the host.
Immunogenicity The ability of a substance to elicit a host's immune response.
Megadata Large volume of patient records derived from physician-supervised treatment and insurance company claims. Sometimes referred to as 'big data'.
Pharmacoepidemiology The use of population-based studies to monitor drug safety.
Pharmacovigilance Scientific and data gathering activities relating to the detection, assessment and understanding of adverse events associated with pharmaceutical products.
Postmarketing After a therapeutic drug has received approval from a regulatory agency.

In recent years, the average worldwide annual market for biologics (including biotherapeutics) was approximately US$157 billion.[a] It has been estimated that it could reach more than US$200 billion by 2016, and the USA represents the largest market of those sales.[a] Oncology and diabetes are the top two therapy areas regarding global spending in medicines.[a] It should be noted that, as opposed to the situation with generics, no dramatic savings are expected in the USA by the introduction of biosimilars. Conversely, the introduction of a biobetter might significantly drive down the cost of the reference product. Notwithstanding market considerations, immunogenicity concerns need to be carefully evaluated for all biotherapeutics.

Anti-drug antibody (ADA) responses can affect safety and/or efficacy of biotherapeutics [11]. In addition, it has been shown that preclinical immunogenicity predictions for endogenous protein sequences can differ from clinical outcomes [12–15]. As reviewed elsewhere, clinical associations between patient genetics (HLA-types) and ADAs have been described [7]. For example, a HLA-DRB1*0701 association with ADAs of the IgG type was identified by testing multiple sclerosis patients treated with betaserum, a marketed interferon-β (IFN-β) that elicits high ADA incidence in humans [13]. Subsequently, even when patients treated with three different IFN-β formulations were included in a larger study, strong associations were observed between HLA types (HLA-DRB1*0401 and HLA-DRB1*0408) and ADAs [14]. In a 2013 draft guidance for industry, the FDA recommended evaluation of genetic factors that might be involved in therapeutic protein immunogenicity.[b] However, the possibility of selecting patients less likely to mount ADA responses against biotherapeutics has been largely ignored, whereas there is great interest in therapy – marker synergies and their correlations with outcomes.

In addition to ADAs, other undesirable components of therapeutic drug immunogenicity can impact product safety [16,17]. Demonstrating a comparable immunogenicity profile in humans is a sensible regulatory criterion for biosimilars when there is no evidence of adverse events (AEs) linked to immune responses for the reference product. However, there are known examples when ADAs emerged in a postmarketing setting, linked to AEs [2,11]. In addition, assay limitations could lead to ADA underestimation in patient samples [13,18,19], and possibly to inaccurate evaluation of ADA associations with AEs. Inaccuracy of assays used to generate data supporting product approval might also complicate the regulatory assessment [19,20]. The complexities of the immune system, coupled with the many factors that can affect immune responses (e.g. patient genetics), make it difficult to predict immunogenicity of therapeutics in large patient populations. Hence, it is not surprising that immunogenicity has been one important issue affecting substitutability of biotherapeutics [2]. The possibility of postmarketing detection of unwanted immunogenicity becomes even more relevant as biosimilars and biobetters are developed and novel therapeutics are approved with postmarketing commitments and requirements–pending concerns.

During the drug development process, safety is evaluated to the extent possible in preclinical studies and subsequently during clinical trials. Limited clinical data might be available by the time some drugs are approved with regulatory requests for further assessment.[c] In the USA and in some other countries, AEs are voluntarily reported during postmarketing surveillance. However, postmarketing spontaneous reporting of AEs might be inadequate for a comprehensive evaluation of long-term drug effects. In addition, the effectiveness of postmarketing (Phase IV) studies has been questioned [21]. Evolving efforts have been attempting to utilize postmarketing patient megadata for concerted drug evaluations [22].

There has been no mechanism in place to compare systematically (in a postmarketing setting) therapeutic drugs approved for the same application regarding their efficacy and associations with the development of malignances and/or other serious diseases.

[a] Report by the IMS Institute for Healthcare Informatics (2012). The global use of medicines: outlook through 2016 (http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global%20Use%20of%20Meds%202011/Medicines_Outlook_Through_2016_Report.pdf; website last accessed on August 6, 2014).

[b] FDA (2013) guidance for industry–immunogenicity assessment for therapeutic protein products. Draft guidance. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf; website last accessed on March 24, 2014).

[c] FDA postmarketing requirements and commitments. (http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm; website last accessed on August 6, 2014).