Comparing Originator Biologics and Biosimilars: A Review of the Relevant Issues

Corrado Blandizzi, MD[1]; Pier Luigi Meroni, MD[2]; and Giovanni Lapadula, MD[3]

[1]Division of Pharmacology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Rheumatology, Ist. G Pini, and Department of Clinical Sciences & Health Community, University of Milan, Milan, Italy; and [3]Rheumatology Unit, Department of Emergence Medicine and Transplantation (DETO), University of Bari, Bari, Italy

ABSTRACT

Purpose: We provide a review of current knowledge on comparability between biosimilars and originator biologics in view of the continuous evolution occurring in this highly dynamic area.

Methods: English-language literature indexed in MEDLINE was explored, without time limits, to July 31, 2016, using the terms *biosimilar*, *biotechnologic drug*, *biologic drug*, *monoclonal antibody*, *fusion protein*, and *anti–tumor necrosis factor*. The reference lists of identified articles were examined carefully for additional pertinent publications.

Findings: Biological medicines are much more structurally complex and extremely sensitive to manufacturing conditions and therefore more difficult to characterize and produce than small molecule drugs. Even minor changes in manufacturing may lead to significant variations of the cellular systems used for biological production, as well as to differences in the structure, stability, or other quality aspects of the end product, all of which have the potential to affect tolerability and/or efficacy and increase the risk of immune responses. Owing to these issues, specific regulatory guidance on biosimilars is continuously evolving, and there is some disagreement on which studies need to be implemented to approve a biosimilar. According to current literature, the following points on biosimilars deserve consideration: biosimilar development is characterized by global harmonization, although several not fully answered questions remain regarding extrapolation of indications, switching or interchangeability, and tolerability; in patients with rheumatic diseases, the tolerability and efficacy of biosimilars in clinical practice remain to be established; several medical and patient associations have published position papers on biosimilars requesting that safety, efficacy, and traceability be carefully considered; long-term postmarketing studies should be implemented to allow physicians to gain confidence in biosimilars.

Implications: On the basis of current knowledge, and taking into consideration both regulatory rules and medical society positions, it can be concluded that, although cost savings are highly desirable, the approval process for biosimilars needs to place tolerability and efficacy, supported by scientifically sound evidence, as the highest priority. Moreover, physicians must retain full authority regarding the decision about which biopharmaceutical to use for treating patients. (*Clin Ther*. 2017;39:1026–1039)

Key words: biologics, biosimilars, comparability, manufacturing, regulatory guidance.

INTRODUCTION

The therapeutic success of biotechnological drugs, commonly designated as biologics, such as monoclonal antibodies (mAbs) and recombinant versions of endogenous proteins, is increasingly transforming the pharmaceutical market. Patent expiry of biologics (ie, originators) has also opened the field to the so-called biosimilars, medicines that are intended to be similar, although not identical, to the originator biologics in terms of quality, efficacy, and tolerability. It is undeniable that there are highly debated issues regarding biosimilars in immune-mediated inflammatory diseases: increasing demand for biologics given their

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clinical success, the nearing of patent expiry for the 4 top-selling biologic brands, and the search for reducing the economic burden of drugs.[1]

A biologic medicine is a large molecule synthesized by cellular systems using recombinant DNA technology and used for treatment, diagnosis, or prevention of various diseases.[2] Current biologics include 3 main categories: (1) products almost identical to endogenous factors, often used as replacement therapy; (2) mAbs that bind soluble or cell surface targets, thus blocking cellular signaling pathways and related functional responses; and (3) engineered proteins mimicking receptors (eg, soluble receptors, receptor antagonists, fusion proteins). Biologics can be from 200 to 1000 times the size of small molecule drugs and are much more complex from a structural standpoint. Biologics are also extremely sensitive to manufacturing conditions and are therefore more difficult to characterize and produce than small molecule drugs.

Unlike generic medicines, in which the active ingredients are identical to their respective originators, biosimilars are similar, but not identical, to their originators. Minor differences among the active ingredients are allowed, provided they are not clinically meaningful. The European Medicines Agency (EMA) defines a biosimilar as a biological medicine that contains a version of the active substance of an already authorized original biologic (reference medicinal product; ie, the originator). Similarity to the originator in terms of quality, biological activity, tolerability, and efficacy, based on a comprehensive comparability exercise, needs to be established.[3]

Steps underlying biologic drug development and manufacturing are highly complex, sensitive to a number of determinants, and specific to a particular product. Even minor changes in manufacturing may lead to significant variations of the cellular systems used for biologic production, as well as differences in the structure, stability, and biology of the end product. Any variation has the potential to affect the tolerability and efficacy of the marketed product, as well as increasing the risk of adverse immune responses.

Of interest, regulatory guidance on biosimilars is continuously evolving, and there is still disagreement on which studies must be implemented to approve a biosimilar. Overall, uncertainties remain the key issue surrounding biosimilars. Policymakers, physicians, and other stakeholders must consider all the issues raised by health authorities in this field. It is crucial to assess how closely similar biosimilars are or are not to their originators and how small differences may affect clinical outcomes.[4] The present article reviews current knowledge on comparability between biosimilars and originators in view of the continuous evolution in this highly dynamic area.

DEVELOPING AND MANUFACTURING OF BIOLOGICS

Biologics comprise a wide array of substances synthesized by cell systems using different processes, including recombinant DNA technology, controlled gene expression, and antibody technologies. To better appreciate differences between originators and biosimilars, it is important to consider the molecular complexity of biologics and their complex manufacturing that involves several steps.

mAbs

Mice were the first source for producing mAbs endowed with high affinity and specificity for their molecular targets. However, the use of rodent mAbs as therapeutic agents has been hampered by their inherent high risk of immunogenicity. Different technologies were then explored attempting to generate low immunogenic mAbs, starting with chimeric antibodies and progressively moving toward humanized and then fully human antibodies.

Technology of Phage Display for Fully Human mAbs

Phage display allows for selection of antigen binding fragments (Fabs) of human mAbs through in vitro procedures, without in vivo steps. It relies on the generation of a library of antibody human genes cloned into the DNA of an *Escherichia coli* phagemid, a bacterial virus that, once introduced into bacterial cells, replicates autonomously, allowing for the biosynthesis of Fabs. On replication, the phage will expose the Fab on its surface and carry the respective DNA encoded in the phagemid DNA. Therefore, with this technique, the genotype and phenotype of specific human Fabs are coupled in the same recombinant phagemid.[5,6]

Technology of Transgenic Mice for Fully Human mAbs

Another technique that has significantly contributed to the development of fully human mAbs relies