Pharmacological Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review Article

Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges

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ARTICLE INFO

Article history:
Received 12 September 2017
Received in revised form 31 October 2017
Accepted 31 October 2017
Available online xxx

Keywords:
Biotherapeutics
Bosimilars
Monoclonal antibodies
Clinical development
Pharmacovigilance
Immunogenicity

ABSTRACT

Second-generation biosimilars (i.e. monoclonal antibodies or proteins generated by fusion of antibody and receptor moieties) differ in several respects as compared to first-generation ones (e.g. epoetins, bone marrow stimulating factors, somatotropins). In this respect, as second-generation biosimilars are endowed with much greater structural and molecular complexity, which might translate into a number of pharmacological and therapeutic issues, they raise new challenges for manufacturers and regulatory authorities as well as new concerns for clinicians. Based on these arguments, the present article was intended to review information on the main differences between first- and second-generation biosimilars for treatment of immune-mediated inflammatory diseases, as well as their impact on immunogenicity, the design of clinical trials and the critical issue of extrapolation of therapeutic indications. The positions taken by relevant medical associations and the crucial role of pharmacovigilance are also reviewed. According to current knowledge, the initial post-marketing clinical experience with second-generation biosimilars is providing encouraging results, though their long-term safety and efficacy as well as the scientific basis underlying the extrapolation of therapeutic indications are still matter of discussion. There is some consensus that marketing applications should rely on studies supporting the clinical use of biosimilars in their different target diseases and patient populations. In parallel, clinical safety must be ensured by a strict control of the manufacturing processes and a solid pharmacovigilance program. It remains then a responsibility of the physician to drive a proper use of second-generation biosimilars into clinical practice, in accordance with guidelines issued by scientific societies.

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Abbreviations: ACR, American College of Rheumatology; ADAb, anti-drug antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; AIFA, Italian Medicines Agency; CDC, complement-dependent cytotoxicity; CHMP, Committee for Medicinal Products for Human Use; DAS28, 28-joint disease activity score; ECCO, European Crohn's and Colitis Organization; EMA, European Medicines Agency; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IG-IBD, Italian Group of Inflammatory Bowel Disease; IMID, immune-mediated inflammatory disease; mAb, monoclonal antibody; PASI, Psoriasis Area and Severity Index; PRCA, pure red cell aplasia; RA, rheumatoid arthritis; SIDeMaST, Italian Society of Dermatology; SIR, Italian Society of Rheumatology; WHO, World Health Organization.

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https://doi.org/10.1016/j.phrs.2017.10.015
1043-6618/

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1. Introduction

Over the last two decades, biotechnological drugs, commonly designated as biologics, have revolutionized the therapeutic management of patients, not only in the field of hormone deficiencies as well as solid and hematologic malignancies, but also in the area of immune-mediated inflammatory diseases (IMIDs), and have become blockbusters for healthcare systems worldwide. After data protection or patents covering biopharmaceutical agents have begun to expire, several biosimilar drugs have been developed and approved for use in different clinical conditions. The term 'biosimilar' was first introduced by the European Medicines Agency (EMA) to describe biologic medicines developed as 'copies' of innovative biologics (commonly designated as originators). However, unlike the generic products of small-molecule drugs, identical copies of biologics cannot be obtained. This limitation depends mainly on the circumstance that biologics are produced by living cell systems, whose biosynthetic processes are subjected to intrinsic and unavoidable factors on biological variability, and partly on their high degree of complexity in terms of both molecular structure and manufacturing procedures. Therefore, the term biosimilar refers to a sort of 'copy' of an authorized branded biologic originator that has demonstrated similarity to the originator throughout the various steps of a rigorous comparative procedure designated as 'comparability exercise' [1,2]. While acknowledging the potential favorable impact of biosimilars on the pharmaceutical market, in terms of both cost saving and drug accessibility, the Italian Medicines Agency (AIFA) has taken the position that originators and biosimilars cannot be considered as interchangeable medicinal products, thus excluding the practice of automatic substitution and switching and, in accordance with the concept of biosimilarity issued by the EMA, emphasizing the principle of the dominant role of clinicians in choosing whether patients should be prescribed with an originator or its biosimilar [3].

Biosimilars, as all biopharmaceuticals, are endowed with highly complex proteic structures and large molecular weight. They are produced through biosynthesis by genetically manipulated living cell systems [e.g. *Escherichia coli* and Chinese hamster ovary cells], which, depending on growth conditions and other factors, can generate mixtures of related molecules that are quite difficult to extract, purify and characterize. Even having access to the exact DNA sequence coding for the originator biologic, it is very difficult to replicate exactly its end-structure (i.e. tertiary and quaternary structures), including post-translational changes, such as glycosylation, and to reproduce exactly the manufacturing process. Accordingly, each biosimilar, even though closely similar to the reference originator, will never reach the level of identity. In this regard, particular attention must be paid, in a regulatory perspective, to the possibility that a biosimilar might display different patterns of immunogenic activity, with a consequent risk of increased propensity to stimulate the production of anti-drug antibodies (ADAbs), as compared with the originator [4–6]. Thus, to cope with the above issues, some regulatory authorities have developed a specific biosimilar approval pathway, first implemented by EMA in 2005, which requires the demonstration of similarity with the respective originator in terms of physico-chemical properties, pharmacology, efficacy and safety, on the basis of a comprehensive head-to-head comparability exercise. If comparison fails at any level, the biologic product is no longer eligible as a biosimilar. Therefore, only the biologic products that display substantial similarity with their respective originators throughout all steps of the comparability exercise can be designated as 'biosimilar' by the regulatory authority and approved for clinical use [7,8]. In this context, an important point of novelty, which has been matter of much debate, pertains to the possibility for a biosimilar product of getting approval for multiple extrapolated therapeutic indications (ideally all those previously granted to the originator), in the face of a clinical development based on a single phase III comparative trial, documenting its similarity with the originator for only one specific therapeutic indication. This is regarded as an issue of high clinical relevance, since it raises the question of whether data obtained with a biosimilar from patients affected by one specific disease are sufficient to allow the use of such a biosimilar in patients with other diseases, for which a direct demonstration of therapeutic equivalence has not been provided by specific clinical trials. In this respect, most experts agree that it is possible that a biosimilar, demonstrated to be effective for one therapeutic indication, is not effective in other indications for which the originator had been previously approved [9–11].

Notably, second-generation biosimilars (i.e. monoclonal antibodies, mAbs, or proteins obtained by fusion of antibody and receptor moieties) differ in several respects as compared to first-generation ones (e.g. epoetins, bone marrow stimulating factors, somatotropins), and therefore they raise new challenges for manufacturers and regulatory authorities as well as new concerns for clinicians. Based on this background, the present article was conceived to review current information on main differences between first and second-generation biosimilars for treatment of IMIDs, as well as their impact on immunogenicity, the design of clinical trials and the critical issue of extrapolation of therapeutic indications. The positions taken by relevant medical associations and the crucial role of pharmacovigilance have been reviewed as well.

2. First-generation biosimilars

The first biosimilars approved by the EMA Committee for Medicinal Products for Human Use (CHMP) were follow-on products of originator biologics endowed with a relatively low molecular weight, including two biosimilars of somatropin, five erythropoietin biosimilars, and seven biosimilars of filgrastim. Since 2006, more than 20 biosimilar products have been introduced into the European market [12]. Filgrastim and epoetin-alpha were the first biosimilars produced for use in hematology-oncology that overcame the strict quality controls and regulatory requirements for approval by the European agency, and have been used for several years as supportive therapy of patients undergoing anticancer chemotherapy [13].

The regulatory pathway for biosimilars introduced into the European market one decade ago has been taken as a reference by other regulatory authorities, including the US Food and Drug Administration (FDA). According to such a pathway, after a biologic product is generated and intended to be highly similar to an originator, similarity has to be demonstrated in both non-clinical (i.e. in vitro and animal testing) and clinical studies. The design of these studies by the proprietary of the biosimilar product is often subjected to preliminary discussion and agreement with the reg-

Please cite this article in press as: C. Blandizzi, et al., Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges, Pharmacol Res (2017), https://doi.org/10.1016/j.phrs.2017.10.015