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Biosimilars in Rheumatology: General Issues

José M. Serra López-Matencio[1], Alberto Morell Baladrón[1] and Santos Castañeda[2*]

[1]José M. Serra López-Matencio, Fellow in Hospital Pharmacy, Hospital Pharmacy Department, Hospital de La Princesa, IIS-IP, c/ Diego de León 62, 28006 - Madrid, Universidad Autónoma, Madrid, Spain

[1]Alberto Morell Baladrón, PhD, Head Hospital Pharmacy Department, Hospital de La Princesa, IIS-IP, c/ Diego de León 62, 28006 - Madrid, Universidad Autónoma, Madrid, Spain

[2]Santos Castañeda, MD, PhD, Rheumatology Department, Hospital de La Princesa, IIS-IP, c/ Diego de León 62, 28006 - Madrid, Universidad Autónoma, Madrid (UAM), Spain

[*]**Corresponding author**: Santos Castañeda, MD, PhD, Rheumatology Department, Hospital de la Princesa, IIS-IP, C/ Diego de León 62; 28006-Madrid, Spain, Tel + 34 915202473; + 34 915202438; Fax: + 34 914018752; Email: santos.castaneda@salud.madrid.org ; scastas@gmail.com

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Editorial

Introduction

The biological market is constantly growing. These drugs have experienced huge advances in very different diseases such as rheumatoid arthritis (RA), diabetes or cancer and it is hoped that they will continue doing so. Although such benefits also come with increased treatment costs, therefore challenging the access and sustainability of health systems. When biologicals licenses have expired, the biosimilars appear, bringing lower prices and thus greater access to health services. Nowadays the biosimilar market is small, representing in 2010 a 3% with respect of the sales of the product reference (somatotropin, epoetin and filgrastim) and a 0.7% of the pharmaceutical market [1]. However, following patent expiry of drugs such as infliximab, adalinumab, etanercept, rituximab, cetuximab, trastuzumab or bevacizumab, the biosimilar market will be enhanced. In Europe is expected that biosimilars cut prices by 20-30% in comparison with the reference products, which will also reduce its price in order to remain competitive, as has already happened with filgrastim or epoetin, whose prices have dropped by 40% in the last few years [2].

What is a biosimilar?

"Biosimilar medicine" or "similar biological" (European Medicines Agency, EMA) or "follow-on biologics" (Food & Drug Administration, FDA) are products designed to have similar action to the reference product that previously has been approved for a particular disease. Biosimilars are not the same as generics (Table 1), which have simpler chemical structures and are considered to be identical to their reference medicines [3]. Biosimilars have been proven, through rigorous clinical trials, to have a high similarity to the reference biological medicine in terms of quality, efficacy and safety [4,5].

Like the reference medicine, the biosimilar has a degree of natural variability. This is because, although DNA sequences its known, variations in the final product can happen due to post-translational modifications (glycosylation, methylation, etc.) inherent to protein molecules, use of different vectors or even environmental changes, which can affect its security or efficacy [6]. Thus, investigation and registration processes differ from those used in generics, so as generics are developed within 2-3 years, carrying out trials with only 20-50 patients and an investment of 2-3 million dollars, getting biosimilars to market needs more time (7-8 years), more patients (around 500), more complex clinical trials and greater investment (100-150 million dollars) [4].

Characteristics	Chemical/generics	Biological/biosimilars
Type of synthesis	Chemical synthesis	Produced by living cells
Size	Low molecular weight	High molecular weight
Structure	Well defined structure	Complex and heterogeneous
Ownership of the production process	Public domain	Owned by manufacturer
Manufacturing process relation	Mostly process-independent	Strongly dependent on the manufacturing process
Characterization	Completely characterized	Impossible to fully characterize
Stability	Stable	Sensitive to external conditions
Immunogenicity	Mostly non immunogenic	Highly immunogenic

Table 1: Main differences between chemical/generic drugs and biological/biosimilars agents.

Manufacturing process

The biological manufacturing process is highly complex and critical in determining the final characteristics of the product. Indeed, it is said that "the process is the product". It begins using cloning vectors to copy relevant genes into living host cells (eukaryotes, bacteria or yeast cells). Once the protein is expressed, the cell is selected and expanded in order to produce a well-defined protein [2,4], then the product is

purified and validated before using. The final product is usually a mixture between different isoforms, in contrast with the homogeneity and uniformity of generic structures.

There are other aspects that can also affect the manufacturing process: their physicochemical instability makes them more sensitive to changes in the environment and thus they tend to form aggregates or to be denatured, needing strictest storage and manipulation conditions [7]. Their huge size and complexity make it impossible to measure accurately the exact amount of each isoform of the biological product, however it is important to identify and quantify chemical and microbial impurities, since they can affect the efficacy, safety and immunological profile of the final product [8].

Regulatory pathways for biosimilars

The European Union has led the way in establishing regulations for biosimilars. In 2005, the EMA established the first regulatory pathway for biosimilars that is distinct from the generic pathway [9-13]. The biosimilar manufacturer should assemble all available knowledge of the reference product with regard to the type of host cell, formulation and container closure system, and submit a complete description and data package delineating the whole manufacturing process including obtaining and expression of target genes, the optimization and fermentation of gene engineering cells, the clarification and purification of the products, the formulation and testing, aseptic filling and packaging.

Furthermore, non-clinical evaluations should be undertaken both in vitro and in vivo. In terms of the clinical evaluation, the comparability exercise should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by the pivotal clinical trials. PK studies should be designed to enable detection of potential differences between a biosimilar and the reference product. Single-dose, cross-over PK studies in homogenous population are recommended. The manufacturer should justify the choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population. PD studies and confirmatory PK/PD studies may be appropriate if there are clinically relevant PD markers, but if there is lack of them, the traditional 80-125% equivalence range is often used. In addition, similar efficacy of biosimilar and reference product has to be demonstrated in randomized and well controlled clinical trials, which should preferably be double blind or at least observer blind. The pre licensing safety data and the immunogenicity data should be obtained from the comparative efficacy trials. Finally, applicants also need to present an ongoing risk management and pharmacovigilance plan, since data from pre-authorized clinical studies are usually too limited to identify all potential side effects of the biosimilar [12,13].

Clinical management

Due to their special characteristics, there is the need to pay even more attention when using biosimilars than when using small chemicals [14]. Most biopharmaceuticals induce immune responses, which in many cases do not have clinically relevant consequences but in some situations the consequences can be more relevant and potentially lethal, causing a loss of efficacy of the drug or even leading to autoimmunity to endogenous molecules [15]. The immunogenicity to biopharmaceuticals is based on their foreign nature, being of exogenous origin (neo-antigens or non-self antigens) or in their similarity to self molecules (self antigens). Anyway, it is the activation of antibody-secreting B cells which is the main reason that causes the clinical manifestation of immunogenicity. There are two ways in which such immunogenicity can occur. On the one hand, impurities, such as endotoxins or denatured proteins within a biopharmaceutical may provide a signal to T cells, that may then send activating signals to B cells and hence, break B cell tolerance. On the other hand, B cell tolerance can be broken via a T cell independent response. If a biopharmaceutical is not uniformly soluble it can form aggregates and they can be confused with viruses, activating B cells to produce auto reactive binding antibodies [16].

Factors leading to immunogenicity of biopharmaceuticals may be product and host related. Product related factors include structural properties, such as protein sequence, the presence of exogenous or endogenous epitopes, the degree of glycosylation influencing protein degradation, exposure of antigenic sites and solubility and other factors such as the formulation and storage, downstream processing, the level of impurity or presence of contaminants [17]. Host related factors include the genetic predisposition of a patient to produce neutralizing antibodies, concomitant illnesses (particularly of the kidney and liver), autoimmune diseases, dose (higher doses or prolonged duration) and route of administration. Immunogenicity appears to be greater if the biopharmaceutical is administered subcutaneously or intramuscularly and has decreasing severity with intravenous administration [18].

This represents a new issue, whether the interchangeability between the original biologic and the biosimilar should be carry out automatically or not [19]. The EMA leave this decision to the respective national authorities [20]. With the approval as a clinically comparable version of the reference product, the biosimilar product should generally be considered as interchangeable, obtaining equivalent outcomes with regards to safety and efficacy with either treatment. The ultimate therapeutic responsibility has to remain with the treating physician based on the verdict of clinical comparability made by the regulatory authority. As for small molecules, a physician should be empowered to exclude individual patients from being switched from one product to another for individual medical or treatment related reasons.

Given their inherent higher variability, record keeping and adverse event reporting, in general, must be more extensive than for small molecule products. It is therefore essential that the tracing of the individual batch that was administered to an individual patient be assured. In other words, pharmacovigilance and traceability are key concepts when managing biological drugs.

Unresolved questions

The reality is that biosimilars in Rheumatology are here to stay. It is a fact that their entry into the global drugs market will be accompanied by a progressive decline in innovator prices, as has already happened in other areas of medicine (e.g. erythropoietin), thereby reducing part of their appeal. Although there are some issues with biosimilars, such as the use of them ahead of the innovator in biologically naïve patients, the switching from existing treatment with original product to biosimilar therapy, the extrapolation of safety and efficacy data in one indication to another (particularly when extrapolation is based on a less sensitive clinical indication such as RA) or in adult patients to pediatrics. All of these issues remain unresolved (Table 2). In addition, it is fundamental to define the different immunogenicity profiles between these products.

Clinical considerations	Product-dependent considerations	Institutional-dependent considerations
Indications	Nomenclature	Substitutions
Evaluation of efficacy & safety using available data	Manufacturing & supply chain	Therapeutic interchange Transition of care Pharmacovigilance
Immunogenicity	Packaging, labeling, & storage	Costs & Reimbursement

Table 2: Main issues remaining unresolved in biosimilar drugs.

In summary, biosimilars represent a breakthrough step; nevertheless there are still several questions to be resolved.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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