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NOVELTIES IN DERMATOLOGY

Biosimilars in Dermatology: Current Situation (Part I)[☆]



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Abstract The first biosimilar version of a biologic agent used to treat psoriasis (infliximab) entered the Spanish market on February 16 of this year, and more biosimilars can be expected to follow in the coming months and years. Logically, this new situation will have economic repercussions and alter prescribing patterns among dermatologists. In this article, we review regulatory issues related to the approval of biosimilars, with a particular focus on the situation in the European Union. We will examine analytical characterization studies and special considerations for clinical trials with biosimilars, and also look at several somewhat contentious issues, such as the extrapolation of indications, interchangeability, and automatic substitution. Finally, we will review the biosimilars with indications for psoriasis currently in the clinical development pipeline and assess their potential to offer comparable efficacy and safety to the reference product while contributing to the sustainability of the public health care system.
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PALABRAS CLAVE

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Biosimilares en dermatología. Situación actual (parte I)

Resumen El 16 de febrero de este año se han comercializado en España los primeros biosimilares de un tratamiento biológico para la psoriasis (infliximab), y en los próximos meses y años está prevista la incorporación de otros biosimilares, con un previsible impacto económico y en los hábitos de prescripción dermatológicos. En la presente revisión se abordan los aspectos regulatorios de la aprobación de biosimilares, con especial referencia al entorno de la Unión Europea, prestando especial atención a la caracterización analítica de la biosimilaridad y las consideraciones especiales referidas al diseño de ensayos clínicos con biosimilares. También se abordan aspectos objeto de cierta controversia, como la extrapolación de indicaciones, la intercambiabilidad y sustitución automática, los biosimilares en fase clínica de desarrollo con indicaciones que incluyen la psoriasis y unas consideraciones finales sobre el potencial de estos fármacos para proporcionar unas alternativas terapéuticas de eficacia y seguridad comparables a las de sus productos de referencia, contribuyendo a la sostenibilidad del sistema sanitario público.

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Introduction

The development of biologic agents in recent decades has substantially improved outcomes in the treatment of psoriasis and psoriatic arthritis, as well as other chronic inflammatory conditions. Drugs such as anti-tumor necrosis factor [TNF] agents and anti-interleukin 12/23 agents have now become available as safe and effective alternatives. However, the elevated cost of their production and marketing, coupled with the fact that some of them have lost or will soon lose patent protection, and the technical feasibility of producing new biosimilar drugs, has prompted an interesting debate with repercussions in medical, social, and public health sectors. The possibility of extending coverage of this type of therapy to a greater number of patients and reducing production costs is one of the most attractive aspects of the arrival of the so-called biosimilars. The health authorities, supported by scientific evidence, need to guarantee that these products are equivalent to their reference biologics in terms of safety, efficacy, traceability, and pharmacovigilance. The present review covers technical aspects of biosimilars as well as the controversies that their arrival is generating in dermatology.

A biologic agent is a drug that contains one or more active substances synthesized or derived from a biological source. Given the complexity of these molecules and the possible variations in their production process, a certain degree of variability is present, even within different batches of the same drug. The European Medicines Agency (EMA) defines biosimilars as “a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’).”¹

The European Union (EU) was the first region to define a legal and regulatory framework for biosimilar drugs (more often referred to simply as biosimilars). The EU lead has been followed by several other countries, such as Australia, Canada, Japan, and the United States, and also organizations such as the World Health Organization (WHO). The first biosimilar was approved by the European Commission

in 2006. In the EU, marketing authorization applications for drugs derived from biotechnology methods (including biosimilars) must be evaluated by the EMA through a centralized procedure. The European Commission then authorizes these drugs on the basis of the scientific opinions issued by the EMA. The resulting marketing authorization is valid in all EU member states. For a biosimilar to be authorized, the applicant must have demonstrated that the differences between the biosimilar and the reference medicine do not significantly impact safety or efficacy, and the biosimilar can only be launched once the patent for the reference medicine has expired.

Biosimilars and Generics

Biologics are obtained from living systems and their exact characteristics and properties depend to a large extent on the manufacturing process. Biosimilars must meet a series of strict requirements in terms of analytic characterization, pharmacokinetic, and pharmacodynamic similarities, as well as efficacy and safety equivalence with respect to the reference product. In contrast, generics are bioequivalent copies with the same active substance, same dose, same pharmaceutical form, same route of administration, and very similar bioavailability. Such products are manufactured using readily reproducible chemical processes. Trials to test therapeutic equivalence are not required prior to approval. Both biosimilars and generics are cheaper than their proprietary counterparts, but biosimilars are normally more complex and expensive to produce, characterize analytically, and develop than generics.² The clinical development program for a biosimilar is cheaper than the original biologic but the pharmacovigilance burden is similar.

Biosimilars are authorized by the competent authorities according to demonstrated comparability with the reference product. The clinical database is limited and often only includes data related to the main indication (or to one of the indications). Biosimilar manufacturers are required

to present all the analytical, preclinical, and clinical data necessary to demonstrate similarity between the biosimilar and reference product.³ Similarity with the original product should be convincingly demonstrated for approval to be granted for indications not directly assessed in the clinical trials with the biosimilar product in a process known as extrapolation.

Interchangeability is the term applied when, in clinical practice, a prescribing physician exchanges or consents to exchange one drug for another in a given clinical context and in any patient with the clinical effect expected to be the same. Replacement is the practice of dispensing a drug in place of another equivalent or changing, without consulting the prescribing physician. The EMA assessments do not include recommendations about the interchangeability or substitution of drugs (including biologics and biosimilars), and leaves the final decision to the member states. In some countries, substitution with a generic is mandatory in certain situations, for example, if the prescribing physician uses the INN. In most member states, however, substitution of one biologic for a biosimilar is not permitted. In the case of biosimilars, once they have been approved, the EMA considers the trade name irrelevant in terms of efficacy, but the trade name and batch number are important for administrative purposes and pharmacovigilance.³

Regulatory Framework

The EMA has drafted scientific, general, and specific guidance by class of product for biosimilar drugs. These are published on a dedicated web page on the EMA website.⁴ Currently, all the biosimilar products approved in Spain can only be obtained from a hospital pharmacy; this situation, analogous to Portugal, differs from other states of the European economic area, such as Germany, France, and Italy.⁵ In clinical practice in Spain, substitution of a biologic drug with a biosimilar drug cannot be done automatically simply because the biosimilar has been approved. A medical prescription is required, as indicated in the decree issued by the Ministry of Health and Consumer Affairs (SCO/2874/2007SSCO/2874/2007).⁶ Biologic products can thus only be substituted under the responsibility of the prescribing physician or in accordance with the internal guidelines of the hospital; however, legislation has yet to be specifically developed for biosimilars.

Degree of Similarity Between the Production Process of a Pharmaceutical Product

Biologic therapies are organic molecules, usually with a high molecular weight, produced in living/organic systems, such as animal or plant cells. The first step is construction of recombinant DNA that encodes the same sequence of amino acids as the reference biologic. This sequence is inserted in a plasmid and transfected into a cell line that produces the new recombinant protein, that is, the biosimilar. The protein is then purified from cell-free supernatant in the culture tank. Impurities in the production process include substances in the culture medium, cell or microbial remnants, DNA used as a template for the product, viral proteins or nucleic acids, enzymes, and salts used in the purification

process. These need to be eliminated. The purified protein is concentrated and transferred to a medium formulation by an ultrafiltration process, in which high molecular weight molecules are retained while smaller molecules are able to pass through the filter.

The characteristics of the final product are determined by the number and sequence of purification steps. Each of these steps requires a process of optimization and control with strict quality control because changes in the culture line, medium, temperature, or purification processes may lead to qualitative changes in the final product. The characterization is not based solely on the number and sequence of amino acids, but also on tertiary and quaternary structure, which may be affected by post-transcriptional modifications that lead to changes in glycosylation and electric charge, as well as potential impurities that may impact both binding of the target antigen (avidity and affinity) as well as biologic immunogenicity. Characterization of biologics and biosimilars by mass spectrometry; glycosylation, acetylation, sulfation, phosphorylation, and glycation (nonenzymatic glycosylation) assays; and electric charge form the basis of fingerprinting analysis for biosimilars and the reference biologic products.

All these characteristics may vary among different batches of the same product, and even within the same production unit.⁷ Manufacturers of biologics monitor post-translational protein modifications whenever there is a change to the production processes. Manufacturers are required to report the bioanalytical data (for example, glycosylation and electric charge) to the health agencies for the batches immediately before and after a change. However, clinical trials do not need to be repeated as these changes are considered to cause minor variations in these characteristics that will not significantly impact the efficacy and safety of the product.

Preclinical trials are also key in assessing the similarity between biosimilars and reference biologics. The affinity and avidity for the target drug should be assessed, as well as the drug's capacity to neutralize the biologic effect of its target in assays based on cell models. Techniques are also being developed to predict the immunogenicity profile in vitro. Finally, a phase I trial is required to establish the pharmacokinetic comparability of the biosimilar with the reference product.

Design of Clinical Trials

Demonstration of biochemical similarity does not necessarily imply functional equivalence. Comparative pharmacokinetic and pharmacodynamic clinical trials are required to demonstrate equivalence of each formulation available in at least 1 phase I clinical trial.⁸ The requirements for demonstrating similar efficacy between a biosimilar and its reference product differ in the EU and the United States, but both regions require at least 1 sufficiently powered equivalence trial to demonstrate comparability of the 2 products in terms of efficacy, safety, and simultaneously, to demonstrate that the biosimilar is not inferior or superior to the reference product.⁹ The EMA prefers parallel-group equivalence trials whereas the FDA recommends that the manufacturer conducts a noninferiority study with a 2-sided test, based

on a prespecified equivalence limit. In certain special circumstances, noninferiority can be based on a 1-sided test. The primary efficacy outcome measure should be clinically relevant and sufficiently sensitive to detect clinically significant differences, but it does not necessarily have to be the outcome measure used in the original pivotal trials. The sample-size calculation for equivalence trials requires a prespecified equivalence margin, or δ , that may or may not be the same as the minimum clinically relevant difference (a statistically significant difference does not necessarily have to be relevant for the patient or physician).¹⁰ The choice of the δ value is largely arbitrary, but the regulators prefer the 95-95 method to determine it.¹¹ In this method, a metaanalysis is used to determine the lower 95% confidence interval for the difference in the absolute risk of response or the hazard ratio between the reference biologic and placebo. δ is then defined as 50% to 75% of that value.

In noninferiority trials, the first hypothesis is tested initially (that is, that the biosimilar is not inferior to the reference biologic) and then the superiority hypothesis is tested. In this design, the noninferiority margin is analogous to that used in an equivalence design. Noninferiority trials have several possible outcomes, which range from inconclusive to statistically or statistically and clinically superior/inferior to the reference product.

According to the requirements of the EMA, the immunogenicity of the biosimilar should be evaluated during the safety trial, whereas the FDA requires a comparative trial before approval and another after the product's launch. Both agencies require implementation of a pharmacovigilance plan. This implies that the biosimilar has to be distinguishable from the reference product even though it is interchangeable in terms of prescribing.

Interchangeability is dependent on biosimilarity, but a product that is biosimilar is not necessarily interchangeable. For the FDA, an interchangeable biosimilar means that "it can be expected to produce the same clinical result as the reference product in any given patient and for a product administered more than once, the safety and reduced efficacy risks of alternating or switching."¹²

In the design of clinical trials for demonstrating interchangeability of a biosimilar (B) with a reference biologic (R), possible prior exposure of the patient to B and/or R should be taken into account. The design should therefore permit assessment of different exposure sequences, taking into account the half-life of the biologic, with the following arms (exposure sequences): RRR, BBB, RBR, BRB, RRB, RBB, BRR, and BBR.¹³ However, a design may be more feasible with the following sequences: RR, BB, RBR, and BRB.¹⁴

Conflicts of Interest

L. Puig has received consultant fees and/or speakers fees from Abbvie, Amgen, Boehringer-Ingelheim, Celgene, Janssen, Leo-Pharma, Lilly, MSD, Merck-Serono, Novartis, and Pfizer, and has participated in clinical trials sponsored by Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer, and VBL.

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E. Esteban Daudén has carried out the following activities: advisory board member, consultant, grant recipient, research support, participation in clinical trials, and paid talks with the following pharmaceutical companies: Abbvie/Abbott, Amgen, Janssen-Cilag, Leo Pharma, MSD, Pfizer, Novartis, Celgene, and Lilly.

S.E. Marrón has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, and Pfizer. He has participated in clinical trials sponsored by Amgen and VBL.

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B. Pérez-Suárez has received consultant fees and/or speaker fees, and/or has participated in clinical trials sponsored by Almirall, Abbvie, Janssen, and Pfizer.

C. Rodríguez-Cerdeira has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, and Almirall.

R. Ruiz-Villaverde has received consultant and speaker fees from Abbvie, Janssen, Merck-Serono, MSD, Novartis, and Pfizer.

J.L. Sánchez-Carazo has received consultant, speaker, and advisory board member fees from Abbvie, Amgen, Celgene, Janssen, Lilly, MSD, Merck-Serono, Novartis, and Pfizer, and has participated in clinical trials sponsored by Abbvie, Amgen, Janssen, Lilly, Novartis, Pfizer, and VBL.

M. Velasco has participated in clinical trials sponsored by Pfizer España and has received consultant and speaker fees from Abbvie, Merck, Janssen, and Pfizer.

The remaining authors declare that they have no conflicts of interest.

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