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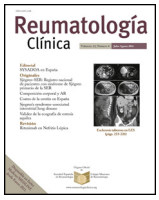

Review Article

Biosimilars: A New Scenario in Biologic Therapies☆

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ABSTRACT

There is no doubt that biologic therapies provide added value for health systems. However, due to their special nature, they also raise some questions that make highly rigorous and demanding quality control and monitoring of their use indispensable. This circumstance is reinforced with the appearance on the scene of biosimilars, which, given their lower cost, are having an increasing impact on the international market. The purpose of this article is to review the major issues posed by their manufacture, distribution and control systems, as well as the most important aspects related to their safety in clinical practice. In this report, we assess the pharmacovigilance of these products, with special attention to traceability, as a key tool to enable earlier detection of adverse events.

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Fármacos biosimilares: un nuevo escenario en las terapias biológicas

Palabras clave:
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RESUMEN

No cabe duda de que los productos biológicos aportan un valor añadido a los sistemas de salud, aunque también plantean grandes interrogantes debido a su especial naturaleza, lo que obliga a ser muy rigurosos y exigentes en su control de calidad y seguimiento. Este hecho se ha visto reforzado por la entrada en escena de los fármacos biosimilares, cuyo menor coste está permitiéndoles alcanzar un mayor protagonismo en el mercado mundial. El propósito de este artículo es revisar en profundidad los principales interrogantes que se plantean en su producción, distribución y control, así como los aspectos más importantes relacionados con su seguridad en la práctica clínica. En este trabajo revisamos lo que representa la farmacovigilancia de estos productos, prestando especial atención a su trazabilidad, como herramienta fundamental para la detección precoz de acontecimientos adversos.

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Introduction

Biological agents represent a great advance in the treatment of complex diseases, such as rheumatoid arthritis (RA), psoriasis, Crohn's disease, multiple sclerosis, diabetes and cancer,[1–4] for which, until they were introduced, we had no really efficient therapeutic options.[5] However, their marked complexity in comparison with drugs obtained by traditional chemical synthesis (Table 1) means that their use requires special care.[6] For this reason, they are included in the list of "medicines under additional monitoring" drawn up for the European Union (EU) pharmacovigilance system.[7] Moreover, we have come to the moment when the patents of some of them are expiring and, with the arrival on the scene of biosimilars, there are a number of questions that we will attempt to address in this review.

Importance of Pharmacovigilance in Biological Therapies

The objective of pharmacovigilance systems is the identification, quantification, evaluation and prevention of the risks of the use of drugs once they have been made commercially available. Therefore,

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Table 1
Differences Between Chemically Synthesized Drugs and Biological Agents.

	Chemical molecules	Biological medicines
Type of synthesis	Produced by chemical synthesis	Produced by live cells
Size	Small molecules (low molecular weight)	Generally large molecules (high molecular weight)
Structure	Well-defined structure and not modifiable once on the market	Complex and heterogeneous structure that can undergo variations after reaching the market
Production process	Production of identical copies regardless of the production process Stages of the production process are well-known	Complex and highly dependent on the production process Stages of the production process protected by patent (property of the manufacturer)
Characterization	Complete characterization	Impossible to characterize in its entirety
Stability	Stable despite external variations	Very sensitive to external conditions (temperature, contamination, handling)
Immunogenicity	Generally nonimmunogenic	Highly or moderately immunogenic

they are designed to make decisions that enable the maintenance in the market of medications in relation to their benefit-risk ratio, or withdraw them from use when this is not possible. It is an activity in which the responsibility is shared among all the agents implied in the use of the drug: holders of the marketing authorizations, health authorities, physicians, pharmacists, nurses and patients, as well as those who assess reports of suspected adverse reactions.[8] For the purpose of defining the bases that establish a quality system, in 2001, the European Medicines Agency (EMA) created EudraVigilance, a network for data processing to evaluate adverse events (AE) reported on the part of regulatory agencies and pharmaceutical companies throughout Europe.

Legislation regarding pharmacovigilance is constantly evolving. On the other hand, the planning of risk management and related activities can vary from one country or region to another, making it difficult to adapt it to the legal framework of each. Thus, the EU created a "risk assessment system" that encompasses all of the activities, and is committed to characterizing and minimizing the possible risks related to a medication. According to it, anyone who applies for the authorization of a medicine is obliged to present a risk management plan (RMP), the purpose of which is to guarantee patient safety, and its update, if considered necessary, can be required at any time.[9]

In the case of biological products, due to their particular characteristics, all of these activities should be done with great meticulousness. In fact, as "a group of medicines under additional monitoring" they include all those biologic products authorized since 2011, a group that they can eventually abandon, like other drugs, once the necessary time has elapsed. More specifically, and because of the complex production process, slight variations in them can affect the final product, even in products with the same active ingredient. Some examples of this are AE associated with erythropoietin, as occurred in 2002,[10,11] with differences reported in the risk of developing factor VIII inhibitors depending on whether second or third-generation products are employed[12] or an increase in the incidence of thrombotic microangiopathy in patients treated with interferon beta preparations with small variations, as was observed with Rebif® and Avonex®. This makes it indispensable to have access to systems capable of detecting any potential distinction in the different biological products, especially for changes produced during manufacture, meaning it is necessary to know the exact batch of each product, as well as the brand name (Fig. 1).

The introduction of the first biological products in clinical practice in Europe brought with it special pharmacovigilance measures, the efficacy of which has been weighed. However, the number has grown a great deal in recent years, mainly due to the large amount of innovative new molecules, but also as a consequence of the arrival on the scene of biosimilar products (Appendix B Supplementary table). This generated a controversial situation centered on the safety and efficacy profiles of the new biological agents, accompanied by continuous debates about them and even on the original products.[13–16] This could all be avoided by guaranteeing compliance with the current legislation and providing proper training in their utilization for all those involved.

There are a number of methods of evaluating the safety of biological drugs, once they become commercially available. The most well-known among professionals is the spontaneous reporting system, based on conveying information on AE that arise during routine clinical practice. At the present time, nearly every country in the world has systems that enable reporting of AE both to health professionals and to the patients themselves.[17] However, very few AE are reported and the quality of the alerts can vary, there being many cases in which we cannot relate a certain AE to a responsible drug without the fear of committing an error. In fact, voluntary reporting of events related to drugs on the part of the hospital staff not is entirely reliable and its level of efficacy differs a great deal from one center to another, as is shown by various studies.[18,19] As an added difficulty, it occurs that, despite the fact that current legislation requires the traceability of the biological medicines utilized, the degree to which this is carried out varies depending on the health center being considered.[20]

This is all very much related to having access to the available information. Thus, for AE that develop over a relatively short time, the essential data can be obtained from the product packaging; but if this has been discarded, the quality of the report will depend on each specific situation. In some cases, for example, physicians may encounter an AE from a medication prescribed by another, and that they do not have access to all the necessary information to carry out a correct clinical decision. In other cases, the patient may not be able to differentiate AE produced from the drug and the symptoms of the disease itself.

Another resource employed includes the electronic databases of the health systems (medical databases and those that collect claims or records concerned with a medication).[21] They have the advantage of ensuring the routine and systematic storage of clinical data. Their availability will depend on the level of development and proper functioning of pharmaceutical records.

Finally, we wish to point out the databases and records kept by the numerous medical associations and scientific societies, which are becoming increasingly important. These vary from small national registries to large international databases that work with multiple treatment arms and focus on a wide range of clinical settings. The majority of these registries are based on selected long-term cohorts that provide information on treatments, as well as on the clinical outcomes obtained, all performed over predefined time intervals. This is the case of the Spanish registry of AE of biological therapies in rheumatic and cutaneous diseases (BIOBADASER and BIOBADADERM, respectively), the British Society of Rheumatology Biologics Register (BSRBR)[22,23] or the European PedNet Haemophilia Registry,[24] to give just a few examples.

On the web page of the EMA we can find all the information referring to the Spanish Pharmacovigilance System, which integrates the activities carried out by health administrations with

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