

# Impact of Biosimilars in Psoriasis Treatment



## Impacto dos Biossimilares no Tratamento da Psoríase

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*Acta Med Port* 2013 Nov-Dec;26(6):646-648

**Keywords:** Biological Agents; Biosimilar Pharmaceuticals; Psoriasis/drug therapy; Portugal.

**Palavras-chave:** Agentes Biológicos; Psoríase/tratamento; Medicamentos Biossimilares.

Psoriasis is an immune-mediated inflammatory skin disease with a profound impact in patient's quality of life.<sup>1</sup> In Portugal, it is estimated that psoriasis affects approximately 250 000 persons. The understanding of psoriasis' immunopathogenesis led to the development of biological therapies that selectively target disease's mechanism of action. As in other fields of medicine, biological therapies revolutionized the treatment of psoriasis, with proven safety and efficacy. These agents are an alternative to conventional systemic therapies and an important tool at the disposal of dermatologist in the management of moderate to severe psoriasis.<sup>2</sup> Currently, it is estimated that approximately 6 000 individuals are eligible for the use of biological therapies in Portugal. The available armamentarium includes: Adalimumab (Humira®, Abbvie), Etanercept (Enbrel®, Pfizer), Infliximab (Remicade®, Janssen Biotech) and Ustekinumab (Stelara®, Janssen Biotech).

The biological therapies, also designated as biologics, are proteins derived from living organisms using recombinant DNA technology.<sup>3</sup> These products vary in terms of their size, structure complexity and immunogenic potential and can be identical to molecules produced by the human body, such as insulin, growth hormone, erythropoietin and monoclonal antibodies that bind to soluble or surface proteins, block pathways or cells, or interact with proteins that mimic cellular receptors.

Unlike chemically synthesized small-molecules, biologics have complex structures of high molecular weight. Therefore, slight changes in the production processes may lead to differences in the final product.<sup>4</sup> Indeed, even different batches of the same product may show a certain level heterogeneity.

The patent expiry of the first generation biologics prompted the development of products with a similar structure as the innovator product, designated as biosimilars, aiming to save costs associated with biologics and increase patients' access to therapies that are especially important in the treatment of chronic diseases.

According to WHO, a biosimilar is a biotherapeutic product which is similar (defined as the absence of a relevant difference in the parameter of interest) in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.<sup>5</sup> Furthermore, the clinical safety and efficacy was demonstrated by adequate preclinical and clinical studies. Biosimilars must ensure similarity with the innovator product regarding some attributes such as the amino acid sequence, conformation, post-translational modifications, immunogenicity, affinity for its ligands and function.

However, biosimilars are not generics, as the later have less complex chemical structures and production processes, being qualitatively and quantitatively equivalent to the innovator product in terms of bioavailability and bioequivalence.<sup>6</sup>

The manufacturers of the innovator product are not required to disclose their manufacturing process after the patent expiry. This gap in knowledge increases the probability of introducing changes in the manufacturing process of biosimilars. In fact, producing an identical copy of a biologic is virtually impossible, due to its structural complexity and heterogeneity. Therefore, it is probable that these differences, especially in the manufacturing process, will lead to differences between innovators and biosimilars.<sup>7</sup>

The ability to produce immune responses through the development of anti-drug antibodies, known as immunogenicity, extends to all biologics, including biosimilars, and this has clinically meaningful implications, especially in terms of safety.<sup>8</sup> Due to potential structural differences between innovators and biosimilars it is possible that the immunogenicity profile can vary between these products.

In July 2012, the Korea Food and Drug Administration approved CT-P13 (Remsima®, Celltrion), the first biosimilar of a monoclonal antibody (Infliximab, Remicade®, Janssen Biotech). In 2013, EMA approved the use of this biosimilar in the EU, based on a sole equivalence clinical trial, conducted in rheumatoid arthritis patients, supported by a pharmacokinetic trial in patients with ankylosing spondylitis.

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Recebido: 18 de Novembro de 2013 - Aceite: 05 de Dezembro de 2013 | Copyright © Ordem dos Médicos 2013

CT-P13 was also granted approval for the other infliximab's indications (Chron's disease, ulcerative colitis, psoriatic arthritis and psoriasis), despite no clinical trials were conducted in these indications.<sup>9</sup>

Considering the complexity of biosimilars and all the implications associated with its emergence, it is crucial that competent authorities, speciality colleges and scientific societies disseminate recommendations regarding its use.

The authors aim to comment and emphasize the most controversial and complex aspects in the context of biosimilars. The authors consider that effective treatments should be made available to all patients at the lowest cost possible. It is expected that due to the expected cost savings biosimilars will increase the access to biologic therapies. However, the highest priority should be given to the patient's safety, so all decision regarding the use of biosimilars and interchangeability should be grounded in sound scientific evidence, and follow several guiding principles:

1. Subtle differences in the production of biologics may impact in their functional properties, either in terms of efficacy or safety. Therefore, for a biologic to be considered "similar" to innovator according to the current EU regulatory framework it should undergo all pre-clinical and clinical steps of the development program.

2. The licensing granted for a particular indication should not be extrapolated to the innovator's other indications without prior minimal efficacy and safety demonstration in the proposed indications. The potential variability between the innovator product and the biosimilar, the different posology regimens, the inherent differences between diseases in terms of their physiopathological mechanisms, the comorbidities and concomitant therapies, do not ensure the same efficacy and safety profile in these different indications. Thus, the results obtained in rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases and other indications, should not be extrapolated for psoriasis and psoriatic arthritis.

3. Similarly to the approval process for the innovator product in a particular indication, biosimilars should be evaluated in clinical trials specifically designed for this same indication, since bioequivalence does not necessarily implicate therapeutic equivalence. So, the extrapolation should be regarded with caution in the absence of the demonstration of efficacy through clinical trials, or when safety is not completely established.

4. Immunogenicity is a primary safety concern of biologics and can also impact in their efficacy and safety profile. Due to the potential variability between the innovator and biosimilar, the immunogenic profile can also be different. Therefore, the investigation of anti-drug antibodies should be a component of clinical trials involving biosimilars.

5. EMA did not provide any specific guidance regarding interchangeability (switch from innovator to biosimilar or vice-versa according to clinician's judgment/decision) and automatic substitution (switch without the intervention of the prescribing clinician), leaving any regulation to the initiative of the state members.<sup>10</sup> The automatic substitution of an in-

novator for a biosimilar or vice-versa should be considered a change of therapeutic and should not be practice without the previous knowledge and consent from the prescribing clinician or without informing the patients. Furthermore, the automatic substitution may compromise the pharmacovigilance programs.

6. The biosimilar should have a specific naming procedure in order to distinguish easily between biologics. This process will allow the healthcare professionals to accurately track the prescribed therapeutic and link the adverse effect to a specific product.

7. After the licensing of a biosimilar it is essential to implement post-marketing surveillance programs to collect safety data and detect potentially meaningful rare adverse effects.

In conclusion, the authors are favorable to the development of biosimilars and their approval from the competent authorities, provided these products follow the highest quality standards in terms of production and development. The biosimilars should also undergo a complete efficacy and safety evaluation, followed by a post-marketing surveillance program. The approval of biosimilars in the treatment of psoriasis and psoriatic arthritis should be substantiated by investigation in these populations in order to ensure the appropriate efficacy and safety patterns. Clinical judgments should be made on an individual basis, based on the patient and disease's circumstances, and always considering the patient's safety as the highest priority.

Finally, due to the inherent complexity of the biosimilars, their potential impact in the patients, clinicians and healthcare system, and in the absence of a regulatory framework, the authors emphasize the need of competent authorities, Speciality Colleges and scientific societies to generate position papers and recommendations regarding the use these agents in Portugal.

## CONFLICT OF INTERESTS

Tiago Torres served as speaker and Advisory Board member for Abbvie, Janssen-Cilag, Leo-Pharma, MSD, Pfizer. Has received investigational grants from Abbvie, MSD e Pfizer; Has participated in clinical trial and observational studies funded by Abbvie, Amgen, Janssen-Cilag, Merck-Serono e Novartis.

Paulo Filipe served as speaker and Advisory Board member for Abbvie, Leo-Pharma, Janssen-Cilag, MSD, Pfizer. Has received investigational grants from Abbvie, Leo-Pharma, MSD e Pfizer; Has participated in clinical trial and observational studies funded by Abbvie, Amgen, Janssen-Cilag, Merck-Serono e Novartis.

Manuela Selores served as speaker and Advisory Board member for da Astellas, Galderma, Janssen-Cilag, Merck-Serono, Novartis, Pfizer. Has participated in clinical trial and observational studies funded by Astellas, GlaxoSmithKline, Janssen-Cilag, Merck-Serono, Novartis e Pfizer.

## FUNDING SOURCES

None stated for this particular work.

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Acta Med Port 2013;26:646-648

Publicado pela **Acta Médica Portuguesa**, a Revista Científica da Ordem dos Médicos

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ISSN:0870-399X | e-ISSN: 1646-0758



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