

# Biosimilars: New guns for the treatment of rheumatological patients?

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## Abstract

The advent of biological therapies in 2000s has represented a real revolution in the treatment of patients affected by rheumatic diseases, but biosimilars represent nowadays a further revolution both from an economic point of view and for the accessibility to treatment for rheumatic patients. The main scientific rheumatological societies have clearly expressed themselves on the biosimilars topic, by highlighting how they represent a great opportunity to contain costs and treat more patients, and these advantages should be accepted by rheumatologists.

The use of biosimilars in different European countries varies widely; in fact, in some of them their use is mandatory (at least in naïve patients), while in other countries it is only recommended. The knowledge and consequently the acceptance of biosimilars are different among patients, and this also depends on the correct medical information on this topic. As more and more biosimilars receive regulatory approval and reach the market, it is essential for health-care professionals to have the right knowledge about them, so that they are properly transferred to their patients. Biosimilars are not identical to the reference product, and clinicians are particularly interested in the safety and effectiveness of switching from the bio-originator to the bio-similar in experienced patients. We will develop these aspects on biosimilars in the present manuscript, for an update on current guidelines in their use in rheumatic patients.

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Key words: Biological therapies; biosimilars; switch; swap; interchangeability; guidelines; recommendations.

Conflict of interest: The authors declare that they have not received any sponsorship or funding from the pharmaceutical companies mentioned in the paper.

Received for publication: 11 April 2019.  
Accepted for publication: 29 April 2019.

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Beyond Rheumatology 2019; 1:3  
doi:10.4081/br.2019.3

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## Introduction

The progress of molecular biology from the early 1980s to the present days has allowed the introduction on the market of many biotechnological products that have been registered at a global level, representing a new frontier for the treatment of complex, disabling diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (SpA), and psoriatic arthritis (PsA).<sup>1-3</sup>

The considerable cost of these treatments limits the access to these therapies for many patients, but the patent license for the first generation of these innovative biological medications has already expired or is about to expire, and this has allowed the commercialization of the so-called *biosimilars*. Biological therapies represent a real revolution in the treatment of several conditions including rheumatic diseases, and the introduction of biosimilars is a further revolution from the economic point of view and for the accessibility to treatment. Biosimilars are an alternative and more affordable therapeutic option for the National Health Service (NHS) and they allow increasing patients' access to therapy, triggering market competitiveness mechanisms and encouraging price reductions. The savings generated in this way can be redirected in order to finance the expenses involved to access new drugs, including new biotechnological ones.

The main scientific societies have expressed themselves clearly on the subject of biosimilars by highlighting how they represent a great opportunity to contain costs, and this option should be accepted by rheumatologists.<sup>4-6</sup>

The use of biosimilars in the countries of the European Union varies widely, as in some countries biosimilar therapy must be used and this is imposed by local regulations, while in other countries the use of biosimilars is only recommended and the rheumatologists can have more freedom of choice in the drugs armamentarium.<sup>7-11</sup> This is for example the case of what happens in Norway and Denmark compared to France and Germany. In fact, six months after marketing the first biosimilar of Etercept (Benepali®), its use was estimated at 65% in Norway and 88% in Denmark, two countries whose health authorities imposed the use of the least expensive biological agent, while the use of biosimilars is only recommended in France and Germany, and in these countries Benepali® was used in 3% and 10% of patients, respectively. Possible causes of this low prescriptive rate could be the fear of that biosimilars may not be reliable replicas of bio-origina-tors and the inadequacy of long-term efficacy and safety data. Moreover, the prescriptive mistrust increased significantly after obtaining remission with a bio-originator.

The knowledge and consequently the acceptance of biosimilars is also different among patients who have received a correct medical information, compared to patients who are not properly informed on these therapies and their differences with bio-origina-tors.<sup>12,13</sup> As more and more biosimilars receive regulatory

approval and reach the market, it is essential for clinicians to have the right knowledge for a correct prescription. Thus, many societies and multidisciplinary groups have developed position papers to guide rheumatologists in the decision-making process when specific biologic therapies are needed.

First of all, it is important to know the different meaning of the terms *biologic*, *generic*, *biosimilar*, *bio-better*, and an *intended copy*, in order to take a correct prescribing decision or substitution of one drug with the other,<sup>14-16</sup> and this is described in Table 1. Then it is also important to understand the production, authorization and biological differences among the molecules available today for treatment of rheumatic diseases, and we will now focus on these aspects of biosimilar therapy.

## Production process

With the term *biosimilar* we refer to a biological product *highly similar* to the reference biologic drug in terms of safety, purity, potency, quality, and efficacy.<sup>14</sup> The two simple words *highly* and *similar* represent the two-faced Janus of the concept of biosimilarity. On the one hand they are the basis of the concept of biosimilar, and on the other hand they create confusion among physicians and patients. For Food and Drug Administration (FDA) and European Medicines Agency (EMA), a biosimilar does not show *any clinically significant difference* to its biological original<sup>15-18</sup> and its biosimilarity is confirmed by comprehensive comparative studies.<sup>19</sup> However, the simple similarity is not enough to reassure patients and clinicians, as they would probably be much more comfortable using the well-known bio-originator and with biosimilar being a generic of reference product.

Unlike small molecules chemically produced, large molecules such as biologic/biosimilar produced from living organisms, are subject to a natural variability of proteins (post-translational modifications, glycosylation, phosphorylation, acetylation...) so they do not have a well-defined structure<sup>17</sup> and this may change at every production cycle also for bio-origimators.

Natural variability, changes in the structure of the molecule, and more complex manufacturing of biological medicines do not allow an exact replica of the molecular micro-heterogeneity. It is also widely known that there are variations also between individual production batches and minor inconsistencies in the production process, not only for biosimilars but also for bio-origimators. For example, Remicade® has undergone several changes during its life and these are also related to the production process, without having a negative impact on its effectiveness or safety.<sup>18</sup> In all cases a strict control of drug production ensures that variations in biosimilars must remain within the boundaries of the originator and must never be clinically significant, thus a well-defined and controlled production process is fundamental to maintain bio-similarity.<sup>20</sup>

It is also necessary to consider that analytical tools have exponentially improved after the commercial approval of the first bio-origimators, being able to detect even slight differences, to analyze the critical quality attributes (CQA) of biosimilars, and to compare them with the CQA of the biological originator of reference. The CQA, unique to each biological, includes features of critical importance such as pharmacokinetics, pharmacodynamics and immunogenicity.

## Authorization process

Both FDA and EMA require deep scientific and clinical analysis and comparison between bio-originator and biosimilar. Since 2006, the year in which the first biosimilars were approved, EMA has opened the way to the regulation of biosimilars approving the greatest number of biosimilars in the whole world, thanks to the development of specific and rigorous guidelines for their evaluation, which stem from a comprehensive head-to-head comparison of the biosimilar and the reference biological medicine. In particular, the authorization of these drugs in the countries of the European Union requires the implementation of the so-called *comparability exercise*, a regulatory process that compares, step by step, the biosimilar and the respective bio-originator in terms of quality, safety, and efficacy

**Table 1. Definitions of terms derived from *Biosimilars - Draft Position Paper - For commentary; Updating position statement from the European League Against Rheumatism (EULAR) Standing Committee of People with Arthritis/Rheumatism in Europe (PARE); March 2018*. <https://www.eular.org/pare.cfm>**

|                           |   |
|---------------------------|---|
| Biologic/biotechnological | A product that contains one or more active substances derived from a biological source or obtained through a biological process   |
| Biosimilar                | A biological product that is highly similar to a reference product in terms of quality, safety and efficacy, purity and potency demonstrated by rigorous comparability exercises  |
| Generic                   | Exact copy of a small-molecule drug, synthesized via chemical means, with structural and therapeutic identity to the reference product  |
| Intended copies           | Copies of the originator, which have not been submitted to a formal regulatory process in line with EMA and US-FDA directives   |
| Biobetter                 | A structurally/functionally altered biological product resulting in improved or different biological activity from the reference  |
| Interchangeability        | Clinical practice of replacing one drug with another that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or <i>vice-versa</i> ) or replacing one biosimilar with another  |
| Substitutability          | Practice of replacing a drug with another one, often cheaper for the National Health System or for the patient, which has the same qualitative and quantitative composition of active substances, the same pharmaceutical form and route of administration and it is bioequivalent to the reference medicine based on appropriate bioavailability studies |
| Substitution (automatic)  | Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level, without consulting the prescriber   |
| Switch                    | Switch from an organic drug to another one with the same mechanism of action ( <i>i.e.</i> from one anti-TNF $\alpha$ inhibitor to the other)   |
| Swap                      | Switch from one biological drug to another, but with a different mechanism of action ( <i>i.e.</i> from one anti-TNF $\alpha$ drug to an anti-IL-6 biologic treatment)  |

EMA, European Medicines Agency; US-FDA, United States Food and Drug Administration; TNF $\alpha$ , tumor necrosis factor-alpha; IL, interleukin.

using preclinical and clinical studies (phase I, phase III). Safety studies are aimed at identifying any difference from the bio-originator in terms of severity, incidence, and nature of adverse drug reactions. An important issue is the immunogenicity of biosimilars, as biological therapies may induce an immune reaction with the development of anti-drug antibodies, and this reaction can influence therapy efficacy. This immunological effect is related to the production of anti-drugs antibodies, their titer and their activity (clearing antibodies vs binding antibodies).<sup>21,22</sup> Two large international studies (multicenter, randomized, double-blind, phase 3/phase 1 respectively) focused on patients with RA (PLANETRA) and SpA (PLANETAS) demonstrated the bioequivalence between CT-P13 (Remsima<sup>®</sup>, Inflectra<sup>®</sup>) and the first Infliximab biosimilar<sup>®</sup> approved in the EU in 2013.<sup>23,24</sup> These studies show high comparability of all major physicochemical characteristics and activity of CT-P13 compared to Infliximab and another infliximab biosimilar (Flixabi<sup>®</sup>, PF-06438179) has also demonstrated bioequivalence in patients with RA.<sup>25,26</sup> As for the biosimilar of Etanercept (ETN), a randomized, double blind, parallel-group, multicenter phase III 24-week study carried out on 596 patients with RA confirmed the bioequivalence of Benepali<sup>®</sup>, its biosimilar.<sup>27,28</sup> Patients with moderate to severe RA, despite methotrexate treatment, were randomized to receive weekly dose of 50 mg subcutaneous Benepali<sup>®</sup> or ETN. The American College of Rheumatology 20% (ACR20) response at week 24, the primary endpoint, was 78.1% for Benepali and 80.3% for ETN. The incidence of treatment-emergent adverse events was comparable (55.2% vs 58.2%), while the incidence of antidrug antibody production at week 24 was lower in the Benepali group (0.7% vs 13.1%). An extensive characterization study demonstrates similarities in efficacy, safety, and immunogenicity in patients with moderate to severe RA in the use of Imraldi<sup>®</sup>, approved by EMA in 2017 as biosimilar of Humira<sup>®</sup>.<sup>29</sup>

The final assessment on similarity falls within the responsibilities of The Committee for Medicinal Products for Human Use (CHMP) of EMA. The clinical studies are designed differently from those for the approval of a new biological drug, because the aim is to demonstrate the essential similarity and not the clinical benefit itself. Furthermore, bio-originators are marketed for specific indications and subsequently their effectiveness can be exported for other purposes. With regard to biosimilars, the current legislation supports the fact that the extension of drug indications can take place by extrapolation, avoiding further indicative clinical studies.<sup>30,31</sup> This can occur only if there is a demonstrated comparability between biosimilar and bio-originator drug, and if the main mechanism of action is the same as the indications supported by clinical studies. In cases where the mechanism of action is different or so complex to involve multiple receptors or binding sites, it may be difficult to establish the contribution of each component to every specific indication. Additional studies may be required to ensure the exact overlap between the two drugs.

## Post-marketing pharmacovigilance

The marketing authorization of any drug, including biosimilars, under the European legislation, may be granted on condition that post-marketing studies are carried out to investigate its safety profile (PASS, post-authorization safety studies) that emerges only when large numbers of patients are treated for a long period. During the experimental phase, in fact, the use of the drug is reserved to a limited and selected number of patients, thus it is not possible to detect any rare adverse drug reaction, or to monitor the

safety profile in real conditions (*i.e.* in the presence of comorbidities or multiple therapies). Even in the post-marketing phase, the immunogenic risk is extremely important.

Immunogenicity is a complex phenomenon that can be related not only to the characteristics of the drug, but also to patients' features. A lower risk of developing immunogenic responses is associated with an immunocompromised more than with an immunocompetent status, and with the topical and intravenous administration more than with the subcutaneous, intramuscular, and short-term treatment. In addition, taking concomitant therapies can influence both positively and negatively this risk of developing an immunogenic response to biosimilar drugs.

Other factors that might influence this immunogenic potential of a biologic drug are structural variations (glycosylation, chemical-physical or post-translational modifications) contamination, formulation and choice of excipients, and conservation.<sup>32,33</sup>

Each company is required to submit a risk management plan (EU-RMP) together with the application for marketing authorization. The EU-RMP must describe in detail the risk management system, the safety profile of the drug also in comparison with the corresponding reference medicine, and the ways in which the producer will monitor the drug safety and efficacy in order to prevent or minimize any risk in the use of the medicine, including possible modifications of the drug efficacy in clinical practice. The EU-RMP must be approved by the competent authorities before the drug is sold on the market, and it must be produced for every originator or biosimilar drug, authorized by EMA or any other competent European national authority.

## The use of biosimilars in clinical practice

Clinicians are extremely disoriented even by another aspect related to biosimilars: interchangeability.<sup>34</sup> Interchangeability refers to the clinical practice of replacing one drug with another one that is expected to have the same clinical effects. This could mean replacing a reference product with a biosimilar (or vice-versa) or replacing one biosimilar with another.<sup>35,36</sup> In the US the terms *interchangeable* or *interchangeability*, referred to a biologic therapy, that is to say that *the biosimilar product can be substituted with the reference product without the intervention of the doctor who prescribed this last*.<sup>37</sup> The interchangeability of a biosimilar with respect to the reference product is established by a specific FDA commission that analyzes the required documentation based on specific criteria defined a priori, and when the biosimilar is defined as interchangeable, the clinician's decision is not required.<sup>37</sup> Instead, substitutability refers to the practice of replacing a drug with another one, often cheaper for the NHS or for the patient, with the same qualitative and quantitative composition of active substances, the same pharmaceutical form, route of administration, and bioequivalence with the reference medicine based on appropriate bioavailability studies. The automatic substitutability (of equivalents) by pharmacists refers to the practice for which the pharmacist has the faculty, or is required to dispense an equivalent and interchangeable drug instead of the prescribed medicine, without consulting the prescriber, in accordance with national or local regulations. The term *switch* refers to the prescriber who decides to replace one drug with another one having the same therapeutic intent in patients who are undergoing treatment.<sup>34</sup> With the term *switch* we indicate the passage from an organic drug to another one with the same mechanism of action, while the term *swap* is

referred to the passage from one biological drug to another one with a different mechanism of action.

As for the important theme of the automatic substitutability of biosimilars, the European legislation has granted autonomy to the competent national authorities of the different Member States, thus resulting in a great diversity of national and local rules that increases confusion.<sup>20</sup>

A key question is: *When is it possible to replace a bio-originator with its biosimilar?* Only FDA requires switching studies to approve the use of a biosimilar, and we are growing our experience in the use of biosimilars from clinical practice. Many safety data on switching strategies come from studies such as the phase IV NOR-SWITCH randomized trial that analyzed switching from the bio-originator Infliximab to the biosimilar CT-P13, with a focus on efficacy, safety, and immunogenicity. Two groups of patients are observed for 52 weeks, one continuing with the bio-originator and the other one switching to its biosimilar. No differences in disease flares and adverse events (including serious adverse events) are observed between the two groups, and this study first demonstrates that switching is not correlated to worse outcomes.<sup>38</sup> The two studies called PLANETAS and PLANETRA have a 1-year open-label extension phase in which two groups of patients were compared: one switching from reference infliximab to CT-P13, and the other one continuing CT-P13.<sup>39,40</sup> In particular, in the PLANETRA study, 302/455 patients who completed the study were enrolled and 158 had received CT-P13 (maintenance group), while 144 received RP (switch group). The response rates at week 102 for the two groups (maintenance *versus* switch) were 71.7% *vs* 71.8% for ACR20, 48.0% *vs* 51.4% for ACR50, and 24.3% *vs* 26.1% for ACR70, respectively. Treatment-emergent adverse events and drug-antibodies occurred in similar proportions in the two groups, and similar results were reported in the phase extension of the PLANETAS study. The Danish DANBIO registry shows interesting data on disease activity after analyzing the effect of non-medical switching from Infliximab to its biosimilar (Remsima, CT-P13) in Danish patients with RA, PsA and SpA. No modification on disease activity before and after the switch (follow-up time=413 days) was observed in most patients,<sup>41</sup> and despite this, 132 (16.5%) patients stopped the drug stating that the reason for withdrawal was lack of efficacy in 71/132 (54%) or adverse event in 37/132 (28%). This difference (*i.e.*, development of lack of efficacy or adverse event) is not necessarily attributable to CT-P13, but it could be an example of what we call *nocebo effect*, which is the effect of negative expectancies by the patient and/or by negative suggestions given by clinicians. Although it is possible that some of the patients who were switched to the biosimilar could have developed *flares* secondary to the *nocebo effect*, it is highly unlikely that all of them experienced this situation. It is more probable that at least some of these patients had a different clinical and safety response to the biosimilar drug due to the intrinsic differences between the biosimilar and the reference bio-original. Switching between an originator and its biosimilar is expected to become common practice, and data on safety of switches with other biosimilar anti-tumor necrosis factor (TNF) alpha inhibitors are now available.<sup>42-51</sup> The EGALITY study is innovative for its design as phase III-confirmatory efficacy and safety-study conducted in patients with plaque-type psoriasis, with frequent switches at short intervals between GP2015 and ETN, did not lead to negative impact on efficacy, immunogenicity and safety. In this study, after completing an initial 12-week period, patients who reached PASI 50 were re-randomized into two groups: to continue GP2015 or ETN treatment

once-weekly, or to undergo a sequence of 3 treatment switches between GP2015 and ETN at 6-week intervals until week 30. After the last switch, subjects in the *switching arm* should remain on the biosimilar therapy. All the efficacy, safety, immunogenicity parameters demonstrate comparable outcomes between pooled switched and pooled continued treatment groups, thus multiple switching between biosimilars must be evaluated in specific registries as for biologic therapies. What is lacking today is the uniformity of guidelines between EMA, different scientific societies in Rheumatology, national agencies and patients' associations. It is a complex topic; thus, several national and international scientific societies have built position papers that tried to give indications on the use of biological and biosimilar therapies. Recently a consensus-based set of recommendations developed by EULAR and ACR has been published for the use of biosimilars in rheumatological diseases. Five overarching principles and eight consensus recommendations were generated,<sup>52</sup> and all societies shared the principles that the correct treatment is based on the decision shared by the rheumatologist and by the patient, who must be given correct information on the use of biosimilars. At the time of treatment choice, the clinician should contribute to an appropriate use of resources for the sustainability of the NHS, but prescription freedom and guidelines should be used and maintained in the decision-making process. Safe and effective treatments should be available to patients at the lowest possible cost, and if we take into account the similarities between biosimilar and bio-originator, the cost component is decisive in the therapeutic choice. The use of biosimilars in drug-naïve patients is another matter of substantial agreement between scientific communities and patients.

In Italy, the Italian Society of Rheumatology showed perplexity on the concept of *secondary naïve* according to *Agenzia Italiana del Farmaco* (AIFA) interpretation. In fact, for AIFA a naïve patient is no longer limited to those who *have not had previous therapeutic exposure*, but it is also extended to those *for whom, according to the clinician's judgment, previous exposures are sufficiently distant in time*. This definition is scientifically questionable in relation to the immunogenic potential of all biological drugs and the possible immune response to a particular drug.<sup>48</sup>

The evidence currently available indicates that the one-time switch between originator and biosimilar is safe and effective, but first of all the safety and the opinion of the patient must be taken into consideration. However, there is no scientific rationale to expect that switching between biosimilars of the same bio-originator would result in a different clinical outcome.<sup>23-64</sup> Existing data suggest that treating a patient with an approved biosimilar is comparable to a patient treated with the bio-originator. However, no study to date has estimated the efficacy or safety of multiple switching between different biosimilars of the same bio-originator, called *cross-switching* therapy (switch among two biosimilars). Results from studies on switch from the original product to its biosimilar are not even transferable to other biologics/biosimilars of the same original product. As long as no studies occur, a switch between different biosimilars is not recommended.

Multiple therapy switches between original product and biosimilars (*repetitive switch, reverse switch, multiple switching*) may even trigger the formation of antibodies due to the potential immunogenic nature of biologics. Every switch theoretically represents an immunogenic risk for antibody formation, especially due to other accompanying substances such as chemical residues from the production process. For this reason, EULAR does not recommend multiple, medically unnecessary therapy switches, as no data are available.

## Conclusions

Thanks to the advent of biotechnological drugs first, and then biosimilars, the therapeutic scenario of many health professionals and rheumatologists in particular, was overwhelmed by a tsunami. Biological drugs have greatly improved the prognosis of highly disabling pathologies such as autoimmune diseases; on the other hand, biosimilars have added confusion in the rheumatological clinical setting, as clinicians still restrain their prescription. The game is played on the two words *highly* and *similar* which define the biosimilar as a product that is *very similar* to an approved reference product with no difference in its clinical meaning. This concept of biosimilarity creates doubts in the scientific community and help is needed for the correct understanding and prescription of such drugs, to use correctly biosimilars to reduce treatments costs, by creating a competitive market, and to treat a larger number of patients, by dissipating inequalities in healthcare.

The number of biosimilars under development has grown and it will grow in the future, as many originators are reaching the patent deadline, and the major national and international scientific societies in rheumatology have published several recommendations, revised periodically, for the use of biosimilars in the treatment of rheumatic diseases.

These recommendations conclude that: i) the biosimilar treatment must derive from a choice shared by physician and patient, but it must also take into account the cost of these therapies; ii) the evidence currently available indicates that switching between originator and biosimilars is safe and effective, but the patients' opinion must always be considered; iii) the effects of multiple switches between biosimilars and their originators should be assessed in dedicated registers; iv) no switch should be performed without the patient's informed consent.

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