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Review

Biosimilars vs originators: Are they the same?

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ABSTRACT

Biological drugs have revolutionised the treatment of rheumatic diseases, and the recent expiry of the patents for many biological agents has generated considerable interest among pharmaceutical companies and regulatory agencies, and led to the marketing of highly similar, low-cost versions known as biosimilars.

The increasing trend of switching patients from effective but expensive drugs to their biosimilar counterparts will have a considerable economic impact in the coming years. However, although this will greatly extend patient access the latest treatments, clinicians, scientific societies and the patients themselves have expressed a number of concerns about their long-term efficacy and safety, as well as the consequences of potentially multiple switches being dictated by economic pressure rather than medical needs.

Thee aim of this review is to evaluate the pros and cons of choosing biosimilars, and whether and when they can really be considered clinically equivalent to the original drugs.

1. Introduction

Biological drugs have revolutionised the treatment of rheumatic diseases [1–3], and the recent expiry of the patents for many biological agents has led to the marketing of highly similar, low-cost versions known as biosimilars. However, ever since the appearance of the first biosimilar, scientific societies, public health bodies, clinicians and patients have all been asking the same questions:

- Are biosimilars the same as bio-originators?
- Do they patient health at risk in favour of mere economic savings?
- Should their use be seen as a concrete and cost-effective means of giving more patients access to treatment?

Scientific societies clarify their positions by means of regularly updated guidelines; the various national health systems have sometimes recommended and sometimes required their use; and clinicians and patients are both under-informed, albeit for different reasons [4]. Consequently, despite the increasing availability of objective evidence, there are still doubts concerning the safety and efficacy of biosimilars, and the effects of (particularly multiple) switches.

2. Biosimilars vs originators: they are the same

2.1. Why is there still so much hostility to the use of biosimilars?

There is no doubt that the introduction of biological drugs has changed the prognosis of many disabling rheumatic diseases, but their considerable cost limits their use. It is therefore not surprising that pharmaceutical companies and regulatory agencies are highly interested in biosimilars as they represent a relatively inexpensive means of providing a large number of patients access to care. The introduction of biosimilars has also triggered market competitiveness and encouraged price reductions, and the savings can be used to finance access to new drugs.

To paraphrase Henry Ford, “Real progress happens only when the advantages of a new technology become available to everybody”, and the principal rheumatological societies have underlined the progress represented by biosimilars and encourage their acceptance by clinicians [5–7].

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2.2. Why biosimilars do not need to be identical to their originators

One of the biggest fears is that a biosimilar is not a generic drug (the size and structure of the molecule would not allow it), but is this really a well-founded problem? As Gillian Woollett put it: "We have always had variations in biology. It was never a problem until the biosimilars arrived and we asked ourselves what 'similarity' means for a biosimilar" [8–11].

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) defines a biosimilar as a biological product that is "highly similar" to its originator, and has "no clinically meaningful differences" from the reference product in terms of safety, purity, potency, quality or efficacy [8–11]. Is it possible that the doubts of clinicians are due the two words "highly similar", and stem from the misconception that biological compounds never vary.

It well-known that large molecules such as biological agents/biosimilars are made from living organisms that are subject to natural variability, and so their structure is not well defined [11]. Variability is an inherent characteristic of all biological products, including bio-originators Furthermore, the exact replication of molecular micro-heterogeneity is hindered by the complex method of producing biological medicines: for example, Remicade® has undergone several changes during its life that are partially related to the production process, none of which have had a negative impact on its effectiveness or safety [12]. Remicade® could even be considered biosimilar to its first self.

2.3. Regulatory approval of biosimilar products

Biological products represent a growing class of therapeutic products, and account for a significant and increasing slice of healthcare costs. Consequently, an abbreviated approval process has been adopted in order to ensure greater public access to safe and effective biological products, and reduce their cost. This does not mean lowering the standards required for approval, and a strict, well- defined, controlled and avant-garde production pathway maintains bio-similarity and ensures that any variations in the biosimilar are never clinically significant [13,14].

Furthermore, improvements have been made to the methods used to analyse a biosimilar's critical quality attributes (CQAs) such as its pharmacokinetics, pharmacodynamics and immunogenicity, and detect any differences from those of its bio-originator. The immunogenicity of biosimilars is important because the therapeutic efficacy of any biological agent can be invalidated if it induces an immune reaction and the development of anti-drug antibodies [15]. Both the FDA and the EMA require rigorous scientific and clinical analyses, and strict comparisons between a biosimilar and its references product, which means that manufacturers have to generate an array of animal, laboratory and clinical data in order to establish bio-similarity.

The European Union has a rigorous regulatory procedure called a "comparability exercise" that ensures a comparison of the quality, safety and efficacy a biosimilar and its originator in phase I-III preclinical and clinical studies. It is expected that the proposed biosimilar product will lead to the same clinical result as the originator, and that switching does not reduce safety or efficacy. The FDA and EMA evaluate each biosimilar case by case in order to decide the data needed to prove bio-similarity and which elements can be ignored as not being scientifically appropriate.

Two large international, multicentre, randomised, double-blind, phase III trials respectively involving patients with rheumatoid arthritis (RA) and ankylosing spondylitis (PLANETRA and PLANETAS) proved the equivalence of all of the main physico-chemical properties and activities of CT-P13 (Remsina®, Inflectra®), the first biosimilars of infliximab that were approved in the EU in 2013 [16,17]; two other biosimilars (Flixabi® and PF-06438179) have also been shown to be bioequivalent in RA patients [18,19]. Bio-equivalence has also was demonstrated for Benepali® (an etanercept biosimilar) [20,21], and Imraldi®, which was approved by the EMA in 2017 as a biosimilar of Humira® [22]. The EMA's Committee for Medicinal Products for Human Use (CHMP) is responsible for the final assessment of bio-similarity in Europe.

Post-marketing studies (known as post-authorisation safety studies or PASS in European countries) are carried out to investigate the safety profile of a biosimilar when large numbers of patients have been treated for an extended period because it is not possible to detect some adverse events or monitor safety profiles in the presence of co-morbidities or multiple treatments during the experimental phase, The risk of immunogenicity is also extremely important because it may be related to the characteristics of the drug or the patient.

Every drug manufacturer in Europe is required to develop a risk management plan (EU-RMP) for each of its drugs before marketing. The plans describe each drug's safety profile, the ways in which the manufacturer will continue to monitor its safety and efficacy, and the actions designed to prevent or minimise any use-related risks, including any variation in efficacy that may be discovered in clinical practice.

2.4. Indication extrapolation

The aim of a biosimilar development programme is to demonstrate its bio-similarity to its bio-originator rather than a clinical benefit. Bio-originators are licensed for specific indications, although they can subsequently also be indicated for other purposes, and the current legislation governing biosimilars states that their indications can be extended on the basis of 'extrapolation': i.e. there is no need for additional clinical studies [23,24], only a demonstration that the biosimilar and its originator are similar and that its main mechanism of action is the same as that appropriate for the indication requested. This means that biosimilar manufacturers do not need to conduct as many long and expensive clinical trials, thus potentially leading to more rapid accessibility, the greater availability of additional therapeutic options, and lower costs. Extrapolation is based on all of the existing data and evidence included in the submission for the biosimilar, as well as the previous safety and efficacy data of the bio-originator, and takes into account various scientific factors of the indication. It does not simply postulate that the data from one carefully studied indication alone is enough for the approval of a different non-studied indication but has to be supported by scientific evidence concerning the mechanism of action, pharmacokinetics, pharmacodynamics efficacy, safety and immunogenicity of the reference product.

2.5. Clinical practice

Clinicians are also extremely disoriented by the question of when to replace a bio-originator with its biosimilar. The FDA requires switching studies before it approves a biosimilar (the word "switching" refers to the replacement of one drug with another for the same therapeutic purpose in patients undergoing treatment) [25,26], and increasing experience of these has come from studies such as the randomised phase IV NOR-SWITCH trial, which analyses switching from originator infliximab to the biosimilar CT-P13, and found no difference in the efficacy, safety or immunogenicity of the two drugs [27]. Comparable efficacy and tolerability was also found during the one -year extension phase of PLANETAS and PLANETRA and several other studies of switching [28–39]. Finally, it is worth pointing out that the loss of effectiveness or the presence of adverse events reported in some post-switching studies may have reflected a nocebo effect [40]: i.e. the patients' negative expectations.

2.6. Conclusions

It can be concluded that many of the worries of clinicians and patients concerning biological agents are due to their incomplete knowledge of the drugs themselves. It is true that a biosimilar is not literally

the same as its originator because it is a 'living' molecule, but there is also changeability between one production batch of a bio-originator and another. The key question is whether this variability has any clinical significance – and so it has not. According to the recently consensus-based EULAR/ACR recommendations concerning the treatment of rheumatological diseases with biosimilars, all patients have a right to safe and effective therapies at the lowest cost, and all clinician have a duty when choosing a treatment to contribute to the appropriate use of funds in order to ensure the sustainability of their national health system [41].

3. Biosimilars vs originators: they are not the same

3.1. Financial not medical reasons underlie the development of biosimilars

Is there a medical reason for biosimilars, or is their existence simply a question of financial pressure? In 2012, the 15 drug compounds with the highest global sales included seven biological agents, four of which (adalimumab, etanercept, infliximab and rituximab) were originators used in rheumatology whose total sales amounted to $ 32.6 billion [42,43]. Moreover, since 2008, an increasing number of arthritis patients all over the world have been treated with biological agents [43–45]: for example, the number of RA patients treated with biological drugs in Hungary increased from 1500 to 3000 between 2008 and 2011 [44]. There is no evidence that any biosimilar is more effective or safer than its originators, and so there is medical reason for prescribing them: it is only a question of financial pressure [42–45].

3.2. Possible issues during biosimilar production and development

Generic compounds are reliable copies of their original synthetic molecules, but bio-originators and biosimilars are very different. Small-molecule medicines have quite a simple and relatively unvarying structure, are stable, and dot give rise to problems of immunogenicity, whereas biological agents are very large and have very complex structures, may be unstable, and show a high degree of structural variability. Furthermore, they are administered parenterally and may be immunogenic [42].

The production of biological agents is a very complex process that includes selecting and cloning DNA; the transfer of genes into bacteria, yeast or mammal cells; fermentation; protein extraction and purification; and finally drug formulation [46,47]. Even small changes in any one of many steps in the synthesis and production of biosimilars can lead to significant differences in the end products [46]. In other words, their key characteristics or "critical quality attributes" (CQA) may vary because post-translational changes may occur during any stage of the manufacturing process and alter the characteristics of a biosimilar beyond the point of biosimilarity, and this may affect its clinical efficacy and safety [47].

All proteins, including biological agents, may undergo biological modifications such as glycosylation, phosphorylation or methylation, and other changes that may occur during production include oxidation, deamidation, proteolysis and aggregation. Any of these changes may greatly alter the 3-dimensional structure of macromolecules, the consequences of which include alterations in antigen binding that affect their biological activity, half-lives, immunogenicity and stability; and these changes may be more evident in biosimilars than their originators [48,49].

Immunogenicity and the production of anti-drug antibodies (ADAs) against biosimilars may be increased not only as a result of molecular structural changes and production-related, but also by factors such as a patient's health, the dosing regimen and route of administration (subcutaneous, intravenous), drug uptake by immune cells, and concomitant medications [50]. The nature of the indication may also be very important: ADAs against rituximab have been detected in only 1.1% of patients with non-Hodgkin lymphomas, but 11% of RA patients, and 23% of patients with giant cell arteritis [51].

Table 1
Differences in the development of originators and biosimilars.

	Biological originators	Biosimilars
Quality	• individual quality assessment	• individual quality assessment • comprehensive comparison with • reference product
Pre-clinical	• full pre-clinical programme	• shortened pre-clinical programme (tolerance, PK/PD)
Clinical	• phase I programme • phase II programme • phase III programme (in all indications) • risk management plan	• phase I PK/PD study • phase III study of one representative • indication and extrapolation • risk management plan

Biosimilars may not go through a full clinical development process. Bio-originators have to undergo pre-clinical, phase I, II and III trials, whereas the development of biosimilars is often "fast-tracked" in order to save time and money, and may omit the phase II stage. In addition, bio-originators have to undergo phase III trials for all indications, whereas biosimilars may be developed on the basis of indication extrapolation [49,52,53].

Table 1 summarises the differences in the quality, and pre-clinical and clinical development of originators and biosimilars [54].

3.3. Regulatory issues

Bio-originators are highly regulated throughout the world in a largely homogeneous manner [42,44,55], whereas the regulatory guidelines concerning biosimilars are far from consistent: for example, some extra-European countries (e.g. Australia, Egypt, Saudi Arabia, Kuwait) follow the EMA guidelines, others (e.g. US, Brazil, Argentina, Korea, Iran) apply the recommendations of the WHO, and yet others (e.g. Russia, China, India) have their own local guidelines. The sometimes-major differences between these guidelines make it more difficult to regulate biosimilars [45].

The WHO regulations require documentation of the manufacturing process, pre-clinical studies with head-to-head comparisons with the reference product, at least one repeated dose pre-clinical toxicity study, a head-to-head single dose clinical PK study, phase III efficacy studies with head-to-head comparisons with the originator, immunogenicity studies in humans, and a pharmacovigilance plan. They also strongly recommend a clinical PD study with head-to-head comparisons with the reference product [47]. For example, such study was conducted with the infliximab biosimilar CT-P13 in comparison with the originator in RA PLANETRA [17], and in AS (PLANETAS) [16]. There are also recommendations concerning the use of biological originators and biosimilars in rheumatological practice. The recent EULAR recommendations state: "…if a TNF-inhibitor fails, another TNF-inhibitor – but not a biosimilar of the same molecule – can be …. effective…*Vice versa*, an effective biological agent should not be switched to another bDMARD for non-medical reasons" [56], and the Hungarian recommendations state: "When choosing a biosimilar product, the following professional and ethical issues need to be considered. An effective and safe original biological agent should not be switched to a biosimilar. That applies to the same or different compounds. When initiating biological therapy, a biosimilar alternative may be considered after the agreement of the patient. Using biosimilars is primarily an economic consideration so that more patients should have access to treatment" [57]. A direct switch to a biosimilar for non-medical reasons is therefore not recommended.

3.4. Clinician dilemmas

There are some controversial issues that may greatly affect clinician decision making, including indication extrapolation, interchangeability and substitutability, and switching [50].

3.4.1. Indication extrapolation

Indication extrapolation is allowed by the guidelines: biosimilars should be tested in one key indication in a phase III trial, but may then be used in the other indications established for the reference product [47]. However, immunogenicity may vary greatly from one indication to another [51], and the structural modifications that may lead to differences in the efficacy and safety of the originator and biosimilar (as described above) cannot be identified if automatic indication extrapolation is applied without proper testing [46,54].

There are significant differences in the use of indication extrapolation in different countries: it is not recommended in Spain, whereas the UK and France decide on a case-by-case basis (indication/ compound). Furthermore, different agencies in Italy have different views: the Italian Society of Hematology and the Association of Pharmacists freely accept indication extrapolation, whereas the Italian Societies of Rheumatology, Dermatology and Gastroenterology recommend caution [42,50].

3.4.2. Interchangeability and substitutability

Interchangeability and substitutability are two different things: interchangeable biological products are expected to have the same clinical effects as the originator, and interchangeability is usually decided by a health or regulatory authority; substitution means that a certain prescribed medicine is replaced by another equivalent medicine, and is typically decided by a pharmacist [50].

As originators and biosimilars are “similar” in terms of efficacy and safety, but not the “same” or “equivalent”, interchangeability and substitutability may give rise to problems. The automatic replacement (substitution) of a reference biological agent by its biosimilar is not recommended in most countries [50], including Hungary [56]. However, once again, there is considerable heterogeneity among local and regional regulations: for example, in the US, interchangeable products may be substituted at pharmacies without the intervention of the prescribing medical professional, whereas Canada does not support this, and Chile and Japan even discourage it. The question is left to the national authorities of many European countries, whereas the national guidelines of some other countries (e.g. Mexico, Brazil, Argentina) do not address the question at all [42,50].

3.4.3. Switching

There may be medical and non-medical reasons for switching between originators and biosimilars. As biosimilars are not “equivalent” to their reference products, switching from an originator to a biosimilars is basically a switch to another biological agent and has the same consequences [42,50,56].

The findings of many clinical trials suggest that consecutive switching leads to the loss of efficacy of biological agents, and a meta-analysis of 41 papers found that switching to a second, third or fourth agent was associated with an increasingly pronounced loss of ACR20, ACR50, ACR70 and EULAR responses, remission and low disease activity in RA patients [57]. The Spanish registry has fond that anti-TNF cycling leads to decreasing continuation rates and a shorter durations of efficacy [58], and a recent Hungarian study has also found that repeated switches of TNF inhibitors decreases drug survival rates [59].

4. Conclusions

It can be concluded that bio-originators and biosimilars are “similar” but definitely not the “same” or “equivalent” as there may be differences in their structure, immunogenicity and a number of other characteristics. Given major differences in the regulations and recommendations of different countries, as well as differences in attitudes towards indication extrapolation, interchangeability and substitutability, and switching, the following factors should be considered before choosing a biosimilar:

- What data are available concerning the (particularly long-term) safety of the biosimilar?
- What is known about its efficacy?
- What direct clinical comparisons have been made between it and its originator?
- Is there any non-financial reason for preferring a biosimilar about which there is so much uncertainty over its reference product?

5. Final remarks

Biological drugs have greatly improved the prognosis of patients with highly disabling disorders, but their excessive cost strictly limit accessibility [60,61]. The recent expiry of the patents for many biological agents has led to the commercialisation of highly similar, low-cost biosimilars that allow more patients to be treated a significantly lower cost. However, mistrust among clinicians restricts their use, mainly because a biosimilar is not an exact copy of its reference product; nevertheless, they are highly similar and their variability is clinically insignificant.

According to the ACR/EULAR recommendations, switching between originators and biosimilars is safe and effective, although the effects of multiple switches should be evaluated in dedicated registers. Finally, as treatment is a shared choice between clinician and patient, no switch should be made without the patient's informed consent.

6. Take-home messages

- Bio-originators and biosimilars are “highly-similar”
- A strict, well-defined, avant-garde controlled production pathway maintain bio-similarity
- The differences between biosimilars and their reference products have no clinical relevance in terms of safety and efficacy.
- Switching does not increase safety risks or decrease effectiveness.
- No data are yet available concerning the effects of multiple switches between biosimilars and their reference products, or the long-term effects of biosimilars.

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